COMPARISON OF RESPONSE TO NEOADJUVANT THERAPY USING MRI TUMOR REGRESSION GRADING IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER BELOW 25 YEARS OF AGE AND ABOVE 25 YEARS OF AGE

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF MD RADIODIAGNOSIS (BRANCH VIII) EXAMINATION OF THE TAMIL NADU DR M.G.R MEDICAL UNIVERSITY, CHENNAI TO BE HELD IN APRIL 2016

CERTIFICATE

This is to certify that the dissertation entitled "Comparison of response to neoadjuvant therapy using MRI Tumor Regression Grading in patients with locally advanced rectal cancer below 25 years of age and above 25 years of age" is the bonafide original work of Dr Shibi Paul submitted in partial fulfillment of the requirement for MD Radiodiagnosis (Branch VIII) Degree Examination of the Tamil Nadu Dr M.G.R Medical University, Chennai to be held in April 2016.

Guide:
Dr Anu Eapen
Professor
Department of Radiodiagnosis
Christian Medical College
Vellore – 632004.

CERTIFICATE

This is to certify that the dissertation entitled "Comparison of response to neoadjuvant therapy using MRI Tumor Regression Grading in patients with locally advanced rectal cancer below 25 years of age and above 25 years of age" is the bonafide original work of Dr Shibi Paul submitted in partial fulfillment of the requirement for MD Radiodiagnosis (Branch VIII) Degree Examination of the Tamil Nadu Dr M.G.R Medical University, Chennai to be held in April 2016.

Head of the Department:

Dr Shyamkumar N K

Professor

Department of Radiodiagnosis

Christian Medical College

Vellore – 632004.

DECLARATION

I, Dr. Shibi Paul, hereby declare that this dissertation entitled “Comparison of response to neoadjuvant therapy using MRI Tumor Regression Grading in patients with locally advanced rectal cancer below 25 years of age and above 25 years of age” is an original work done by me in partial fulfillment of the requirement for M.D Radiodiagnosis (Branch- VIII) Degree Examination of The Tamil Nadu Dr M.G.R Medical University, Chennai to be conducted in April, 2016.

Candidate:

Dr. Shibi Paul,

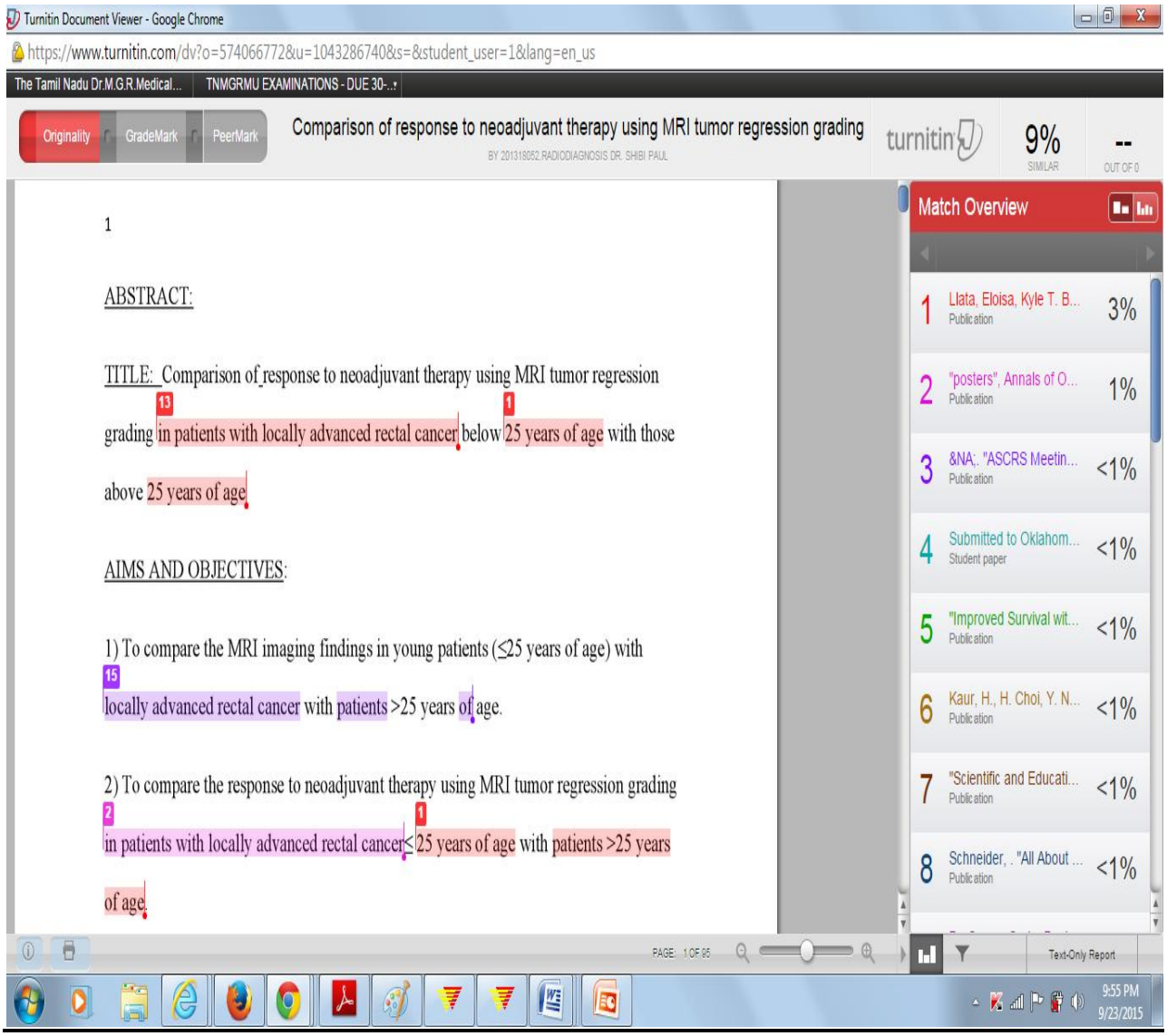
Post Graduate Resident,

Department of Radio Diagnosis,

Christian Medical College & Hospital,

Vellore - 632004.

ORIGINALITY CERTIFICATE:



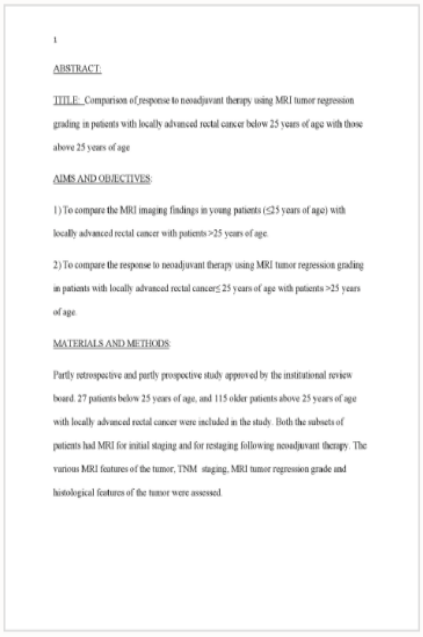
turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201318052.radiodiagnosis Dr. Shib...
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	Comparison of response to neoad..
File name:	check_thesis.docx
File size:	11.72M
Page count:	95
Word count:	9,391
Character count:	50,991
Submission date:	23-Sep-2015 12:02AM
Submission ID:	574066772



1

ABSTRACT:

TITLE: Comparison of response to neoadjuvant therapy using MRI tumor regression grading in patients with locally advanced rectal cancer below 25 years of age with those above 25 years of age

AIMS AND OBJECTIVES:

1) To compare the MRI imaging findings in young patients (≤25 years of age) with locally advanced rectal cancer with patients >25 years of age.

2) To compare the response to neoadjuvant therapy using MRI tumor regression grading in patients with locally advanced rectal cancer≤ 25 years of age with patients >25 years of age.

MATERIALS AND METHODS:

Partly retrospective and partly prospective study approved by the institutional review board. 27 patients below 25 years of age, and 115 older patients above 25 years of age with locally advanced rectal cancer were included in the study. Both the subsets of patients had MRI for initial staging and for restaging following neoadjuvant therapy. The various MRI features of the tumor, TNM staging, MRI tumor regression grade and histological features of the tumor were assessed.

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

January 05, 2015

Dr. Shibi Paul
PG Registrar
Department of Radiodiagnosis & Imaging
Christian Medical College, Vellore 632 004

Sub: **Fluid Research Grant Project:**
Comparison of response to neoadjuvant therapy using MRI tumor regression grading in patients with carcinoma rectum below 25 years of age and above 25 years of age.
Dr. Shibi Paul, Dr. Anu Eapen, Dr. Anuradha Chandramohan, Radiodiagnosis & Imaging, Dr. Benjamin Perakath, Surgery 2, CMC, Vellore.

Ref: IRB Min No: 9038 [OBSERVE] dated 04.09.2014

Dear Dr. Shibi Paul,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Anu Eapen, Radiodiagnosis & Imaging, CMC, Vellore.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit
a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 84,200/- INR (Rupees Eighty Four Thousand Two only) will be granted for 18 months.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Anu Eapen, Radiodiagnosis & Imaging, CMC, Vellore.

IRB Min No: 9038 [OBSERVE] dated 04.09.2014

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

ACKNOWLEDGEMENTS

This study would not have been possible without the help and hard work of many individuals. I wish to place in my record my sincere appreciation and immense gratitude to some of them mentioned below.

I am deeply indebted to my guide Dr Anu Eapen for her continued support, encouragement and valuable guidance in performing this study.

I would like to express my gratitude to Dr Anuradha C., Dr Benjamin Perakath and Dr Jacob for their guidance and help in this study. I would also like to thank Dr Gayathri for her help with the diagram's and Mr Bijesh Yadav and Ms Anna Varghese for their help with statistical analysis.

I am grateful to all the patients who formed part of this study, without whom this would not have been possible.

I am thankful to the staff in the Department of Radiology, MRI technicians and the doctors from the department of colorectal surgery for their help.

Above all, I am thankful to God, my parents and my colleagues for their constant help and encouragement during this endeavor.

CONTENTS

ABSTRACT:

TITLE: Comparison of response to neoadjuvant therapy using MRI tumor regression grading in patients with locally advanced rectal cancer below 25 years of age with those above 25 years of age.

AIMS AND OBJECTIVES:

1) To compare the MRI imaging findings in young patients (≤25 years of age) with locally advanced rectal cancer with patients >25 years of age.

2) To compare the response to neoadjuvant therapy using MRI tumor regression grading in patients with locally advanced rectal cancer ≤ 25 years of age with patients >25 years of age.

MATERIALS AND METHODS:

Partly retrospective and partly prospective study approved by the institutional review board. 27 patients below 25 years of age and 115 older patients above 25 years of age with locally advanced rectal cancer were included in the study. Both the subsets of patients had MRI for initial staging and for restaging following neoadjuvant therapy. The various MRI features of the tumor, TNM staging, MRI tumor regression grade and histological features of the tumor were assessed.

RESULTS:

On bivariate analysis, the incidence of tumors with MRI T2 high signal intensity in patients ≤ 25 years of age was higher, 48.1 % compared to 19.3% in patients >25 years of age (p = 0.002). The incidence of poor response to neoadjuvant therapy (by MRI tumor regression grade) was significantly more common in younger patients (66.7%) compared to older patients (40.9%) (p = 0.01). Also, in tumors which showed poor response, there was significant increase in the incidence of T2 high signal tumors (p = 0.00) , EMVI positive tumors (p=0.001), mucinous tumors (p = 0.015) and poorly differentiated tumors (p = 0.00) and T2 high signal in MRI (OR, 6.28; 95% CI,1.48-26.55) and presence of EMVI (OR, 4.17, 95% CI, 1.55-11.19) were found to be two independent predictors for poor response.

CONCLUSIONS:

Patients younger than 25 years of age were more likely to have poor tumor regression grades. Factors like age less than 25 years, T2 high signal intensity, presence of EMVI, mucinous tumors and high grade tumors were significantly associated with poor response to neoadjuvant therapy. T2 high signal intensity of tumors on MRI and presence of EMVI were found to be two independent predictors for poor response.

INTRODUCTION:

Colorectal cancer is one of the foremost causes of deaths due to cancer worldwide (1) There are several risk factors attributed to this cancer, both genetic and environmental. The stage of the disease at presentation influences the prognosis and survival rate. Rectal cancer is known to occur commonly in patients more than 50 years of age with significant increase in the incidence above 60 years of age (1).

An increase in the incidence of rectal cancer has been noted among younger patients recently. Many of them present with an advanced stage of disease and do not have a family history (2). There was also a significant increase in the incidence of mucinous tumors in younger patients compared to older patients (3). Also, the survival of patients with mucinous cancer was worse than non-mucinous tumors, with poorer prognosis among those patients with metastatic mucin producing tumors (4)(5).

With the advent of 3Tesla MRI, local staging of rectal cancer has become more accurate; with use of high resolution T2 weighted images (6)(7).

Patients with locally advanced rectal cancer will require neoadjuvant therapy in order to reduce the local recurrence and to downstage the disease so that surgery is feasible. MRI with

high resolution imaging is the preferred mode of imaging to assess the response to preoperative therapy.

To assess the response to neoadjuvant therapy , a grading system based on MRI findings was devised by MERCURY study group which closely reflected the pathological tumor regression grading (8). This MRI Tumor Regression Grading system was found to predict the survival outcome and also aided in planning further treatment before surgery (9).

We proposed to assess the response to preoperative therapy using MRI Tumor Regression Grading in locally advanced cancer patients younger than 25 years of age compared to older patients.

AIM:

To compare the response to neoadjuvant therapy using MRI Tumor Regression Grading in patients with locally advanced rectal cancer ≤ 25 years with patients >25 years of age.

OBJECTIVES:

1. To compare the MRI imaging findings of young patients (≤25 years of age) with locally advanced rectal cancer with older patients (>25 years of age) with rectal cancer.

2. To compare the response to neoadjuvant therapy using MRI Tumor Regression Grading in patients with locally advanced rectal cancer ≤25 years of age with >25 years of age.

JUSTIFICATION OF THE STUDY:

The incidence of rectal cancer is on the rise among younger patients as per the recent studies (3). They present with advanced disease and have more mucinous cancers and high grade tumors which are known to be associated with bad prognosis (4). Many of them may not have a family history and as the index of suspicion is low, the diagnosis may be made late (2). The incidence of mucinous cancers in younger patients range from 10.8% to 16% in western studies (3). A study from our centre has reported an incidence of 35.5% of patients younger than 40 years of age among those with rectal cancer; however they showed the long term outcome was comparable (10). Till date, no studies are done in patients younger than 25 years of age.

Many of the young patients present with locally advanced tumor and hence undergo neoadjuvant therapy. The patients whose tumor does not regress may not undergo surgery. MRI examination with high resolution imaging is advocated in rectal cancers for accurate local staging at presentation and also to assess response to neoadjuvant therapy (8).

MERCURY group has devised a tumor regression grading based on MRI which closely reflects the pathological tumor regression grading. Studies have shown that poor MR tumor regression grade is associated with poor survival rates and more local recurrence rate (9).

The purpose of our study was to evaluate the response to neoadjuvant therapy in patients $\leq$ 25 years of age on the basis of MRI tumor regression grading and to compare it with patients>25 years of age.

MATERIALS AND METHODS:

STUDY DESIGN: Part retrospective and part prospective study,

STUDY TYPE: Observational study

STUDY SETTING:

Christian Medical College (CMC), Vellore is a tertiary care hospital in Tamil Nadu, situated 119 km from Chennai. The centre was established in 1900 and is now a teaching and referral centre. It is a 2700 bedded hospital. The average annual outpatient visits are 2 million and in-patient admissions are 1,30,000. The patients come from both southern and northern states of India, and a few of them also come from the neighboring countries, Nepal and Bangladesh. The Department of Radiology was established in the year 1936 in CMC. The department was digitalized and made filmless when PACS (Picture Archival and Communication System) was introduced in 2000. There are around 80 radiologists in the department. Around 7,30,815 examinations were performed in the year 2014-2015 among which 39,101 were MRI studies.

STUDY POPULATION:

INCLUSION CRITERIA:

1. All consecutive patients $\leq$ 25 years of age with histopathologically proven rectal carcinoma who underwent MRI in Department of Radiodiagnosis for primary staging and for evaluation of response to neoadjuvant therapy from January 2012 to June 2015.

2. Every second patient > 25 years of age with histopathologically proven carcinoma rectum who underwent MRI in the department of Radiodiagnosis for primary staging and for evaluation of response to neoadjuvant therapy from January 2012 to June 2015.

EXCLUSION CRITERIA:

1. All patients with carcinoma rectum who had undergone CT for primary staging or who had undergone imaging elsewhere

2. All patients who had defaulted treatment; or were lost to follow up after the initial scan for primary staging

3. All patients who had undergone definitive treatment like surgery, chemotherapy or radiation therapy elsewhere at presentation.

Sampling and consent:

For the group of younger patients with rectal cancer (≤25 years of age), all consecutive patients with rectal cancer who underwent MRI in the department of Radiology for primary staging or follow imaging to assess response to neoadjuvant therapy from January 2012 to June 2015 who fulfilled the inclusion criteria were recruited. For the group of older patients with rectal cancer (> 25 years of age), every second patient > 25 years of age who undergo MRI the department of Radiology for

primary staging from January 2012 to June 2015 who fulfilled the inclusion criteria were recruited. Those who had rectal cancers other than adenocarcinomas and those who had initial staging MRI elsewhere or CT as initial imaging or for re-staging were excluded from the study.

Informed written consent was obtained from the patient before the MRI examination. The data of the patients was entered into a numbered proforma (Appendix 1).The informed consent form along with the patient information sheet is attached in Appendix 2.

Role of neo-adjuvant therapy:

Preoperative therapy was administered to the patients with locally advanced tumor so that the tumor was downstaged. The various types of preoperative therapy included short course chemoradiation, long course chemoradiation and chemotherapy alone. Long course chemoradiation was most commonly administered in patients with locally advanced malignancy to downstage the tumor. 50.4Gy radiation therapy was administered in 28 fraction (#) along with concurrent Capecitabine 825mg/m^2 which was given as tablets orally twice daily or with 5-Fluorouracil, in long course chemoradiation. In short course radiation regimen, 25 Gy was administered in 5#.

Timing:

The re-imaging to assess response to neoadjuvant therapy was usually done six weeks from the neoadjuvant therapy.

MRI EXAMINATION:

a) MRI scanner

Both the initial staging MRI and re-staging MRI were performed in a 3 Tesla MRI scanner (PHILIPS systems Achieva).Both MRI abdomen and MRI pelvis were done in the patients. Most of the patients had MRI pelvis for re-staging.

Photograph of the 3 Tesla MRI scanner

b) MRI coil:

SENSE XL TORSO coil was used which is a 3- Tesla wrap around coil with 16 elements; 8-element anterior coil and 8-element posterior coil.

Photograph of the MRI coil

c) MRI protocol:

Sequences:

- T2 axial and coronal

- T1 axial

- T2 SPAIR axial

- T2 HR coronal, axial and sagittal

- DWI axial along with corresponding ADC

Techniques:

i) Localiser scan (Sagittal, coronal and axial planes)

ii) MRI sequences

1. T2W SPAIR axial

   (TR – 865ms; TE – 70ms; Flip angle – 90^0; matrix 284 x 17)

2. T2W transverse

   (TR – 1097ms; TE – 80ms; Flip angle – 90^0; matrix 300 x 193)

3. T1W transverse

   (TR – 12ms; TE – 2.3ms; Flip angle – 15^0; matrix 256 x 153)

4. T2 HR transverse

   (TR – 3500ms; TE – 90ms; Flip angle – 90^0; matrix 320 x 243)

5. T2 HR coronal

   (TR – 5067ms; TE – 80ms; Flip angle – 90^0; matrix 328 x 309)

6. T2 HR sagittal

   (TR – 3836ms; TE – 80ms; Flip angle – 90^0; matrix 316 x 275)

7. Gradient 2D diffusion weighted transverse

   (Diffusion mode – 3 scan trace; Diffusion weightings – 3; b value 1 = 50; b value 2 = 400; b value 3 = 800; Trace weighted images; Average ADC maps; EPI factor – 142; TR – 9700ms; TE – 79ms; slice thickness 6mm with slice gap 1.2mm; FOV – 47.5cm; matrix 142x192; one acquisition scan time ~3.24 minutes)

d) Image interpretation

The images were interpreted by an experienced radiologist who was given only the staging and re-staging MRI images. The radiologist who was interpreting the images was blinded to the histological diagnosis or any other details about the patient. T2W high resolution coronal, axial and sagittal sequences were used in interpreting the local staging.

INSTITUTIONAL BOARD APPROVAL AND FUNDING:

The approval of the institutional review board was obtained before starting the study (IRB Min no:9038 dated 04.09.2014)

STATISTICAL ANALYSIS:

Statistical analysis was performed using SPSS software, version 18.

The association between various tumor characteristics in younger (≤25 years of age) and older (> 25 years of age) age groups and in the good tumor response (MRI tumor regression grade 1-3) and bad tumor response (MRI tumor regression grade 4-5) groups were analysed using Pearson's Chi square test.

The factors predicting the bad response outcome were analysed using multivariate regression analysis.

P value of <0.05 was considered as statistically significant.

REVIEW OF LITERATURE:

EPIDEMIOLOGY:

The global epidemiology:

Colorectal cancer is the third commonest malignancy worldwide (11). Globally, about 9.4% of cancers in men and 10.1% cancers in women are found in the colorectal region (1). Around 12 lakh new cases of colorectal cancers were detected in the year 2012 alone (11). Most of the tumors in colo-rectal region occur in rectum (82). Among the tumors in colorectal region, 95% are adenocarcinomas. The other types of cancer affecting rectum include squamous cell carcinomas and neuroendocrine tumors (11). Colorectal cancer is the fourth leading cause of death due to cancer worldwide. In the year 2002, about 530,000 died due to colorectal cancer (12). The highest incidence of colorectal cancer is seen in Australia and Europe whereas the lowest incidence is seen in Africa and Central Asia (13). The stage of the disease at presentation determines the prognosis and survival rate (12).

The Indian epidemiology:

The incidence of colonic malignancy is 0.7 to 3.7 per lakh in males and 0.4 to 3 per lakh in females, in India. The incidence of rectal tumors is 1.6 to per lakh in males and 0 to 2.8 per lakh in females, as per eight population registries (13)(14)(15).

Even though the incidence is low, the number of cases in India is high because of the huge population.

RECENT TRENDS:

Recently, it has been noted that the incidence of rectal cancers in young patients is on the rise and they present commonly with mucinous tumors and in advanced stage (3)(16)(83) Studies have reported an incidence of 13.3% of young patients (<40 years of age) among those with rectal cancer (17).Young patients with rectal cancer with no known genetic predisposition presented with advanced stage of disease (2).There was significant difference in the incidence of mucinous tumors among the younger and older patients with rectal cancer; that is, 16% of young patients had mucinous tumor versus 4% of mucinous tumor in older patients (17). Survival of patients with mucinous cancer was worse than non-mucinous tumors, with poorer prognosis among metastatic mucin producing tumors. Young patients also presented with advanced stage disease (84)

Data from our institution showed a significantly higher incidence (35.5%) of rectal cancer in patients younger than 40 years compared to western studies and also these patients presented at advanced stage (10). However stage wise survival and prognosis was not significantly different among patients younger than 40 years of age and older patients (10)(18)(19).

Most of the studies which have compared survival and prognosis of young versus old rectal cancer patients have grouped their patients as those < 40-50 years of age and older.

We, in our institution, have noticed that very young rectal cancer patients present with advanced stage and respond poorly to treatment. There are no studies till date which has looked at patients younger than 25 years separately.

RECTAL ANATOMY:

The rectum is about 12-15cm long and is located in the distal portion of alimentary tract which starts at the rectosigmoid junction extending distally till the upper anal canal at the level of the insertion of puborectalis where it forms the puborectalis sling. The rectum is divided into three parts- upper, mid and lower rectal segments. The distal 5 cm is low rectum, middle 5cm is mid rectum and the proximal 5cm is upper rectum (20)(21).A fat tissue containing structure named mesorectum surrounds the rectum. The contents of the mesorectum include lymph nodes and vessels. The mesorectum is limited by mesorectal fascia (20)(17).

RISK FACTORS:

The incidence of colorectal cancer increases after the age of 40 with a sharp rise after 50 years of age (82). Recently, an increase in the number of cases of rectal cancer among adults with no known risk factors has been note (3)(4). The screening programmes are usually aimed at younger patients with risk factors or older patients, making this new trend worrisome.

Multiple risk factors are known to be associated with colorectal malignancies, both genetic and environmental. Rectal cancer has a mild predilection to male gender (20).

The various predisposing factors of colorectal malignancies include hereditary non-polyposis colon cancers, familial non-polyposis syndromes , and inflammatory bowel disease (4)(22) . About 70% to 75% of patients have sporadic disease (23).

The environmental factors include dietary factors like consumption of red meat, physical inactivity, abdominal obesity etc (24)(23). Life style practices like consumption of more dietary fiber, decreasing the consumption of red meat and exercise are proposed to be beneficial in decreasing the risk of rectal cancer (24)(23).

The tumors are termed as upper, mid and low rectal tumors depending on the site of involvement in rectum. One-third of rectal tumors occur in upper rectum, one-third in mid –rectum and one -third in low rectum (25). The low rectal tumors can involve the anal sphincter complex and hence may require neoadjuvant therapy for downstaging the disease before surgery.

Adenocarcinomas constitute most of the rectal tumors. The variants of adenocarcinoma are mucinous adenocarcinoma, signet ring cell adenocarcinoma and medullary carcinoma. When more than 50% of a tumor consists of extracellular mucin, it is termed as mucinous adenocarcinoma. Signet ring cells are cells with intracellular mucin and those tumors which have more than 50% signet ring cells are known as signet ring cell adenocarcinoma (26). Mucinous cancers formed about 38.5% of all colorectal tumors (27). Most of them are high grade tumors. Mucinous tumors and signet ring cell tumors usually present at advanced stage(stage III/ stage IV)- 80.9% of signet ring cell and 52.8% of mucinous tumors; and are also likely to respond poorly to neoadjuvant therapy

with only 23% of these tumors showing downstaging following therapy (28)(29). The five year survival rates in mucinous tumors are also poor- 11.9% in signet ring cell tumors and 49.4% in mucinous tumors (30).

The tumors can further be graded into well, moderately and poorly differentiated, based on histology. Poorly differentiated tumors are further associated with bad survival rates. High grade tumors were associated with more rates of local recurrence (31).

The involvement of mesorectum, the depth of extramural invasion by the tumor and involvement of anal sphincter complex is crucial in deciding on the management of rectal malignancy. The stage of the disease at presentation determines the survival rate (26).

In early tumors (T1, T2, T3 with negative CRM and no significant nodal disease), surgery is offered.

Multimodality treatmentwhich consists of surgery, radiation therapy and chemotherapy is usually offered to patients with locally advanced rectal tumors (32).

In locally advanced rectal tumors, where mesorecta linvolvement and mesorectal lymph nodes are present, neoadjuvant therapy is advocated pre-operatively. Either short course or long course radiation therapy along with chemotherapy or chemotherapy alone can be administered as part of neoadjuvant treatment (33). Long course chemoradiation is the commonly used type of neoadjuvant therapy in locally advanced disease.

Neoadjuvant therapy in rectal cancer is aimed at

- downstaging the tumors prior to surgery

- preventing local tumor recurrence

- enabling sphincter sparing surgery when possible.

Abdominoperineal excision is done in low rectal tumors when sphincter sparing surgery is not possible. Patients with upper and mid rectal tumors undergo anterior resection.

Patients with T1 or T2 disease undergo local surgery; whereas those with T3 with negative CRM and no significant nodal disease undergo total mesorectal excision.

Before the era of total mesorectal excision (TME), anterior resection and abdominoperineal excision was performed as curative procedures. However, the rate of local recurrence was about 16.3% which has significantly reduced to 8.3% with the introduction of total mesorectal excision (34)(35).The local recurrence is attributed to the involvement of mesorectal fascia which was not removed completely during traditional procedures and hence the concept of total mesorectal excision was introduced where sharp dissection is performed along the plane of mesorectal fascia to ensure block dissection of lymphatic channels in the rectum (36)(34). After the tumor is resected, depending on the tumor present in the margin of the resected tissue. If no tumor is present in the margin, then it is R0 resection and is curative. R1 resection has microscopic tumor and R2 resection has visible tumor and both resections are considered palliative (37)(38).

The rate of local recurrence following surgery alone was further reduced by pre-operative radiation therapy wherein the local recurrence rate after a median follow up of two years was 2.4% compared to 8.3% when there was no neoadjuvant therapy (34).

Multiple studies have shown that the chance of achieving R0 resection when neoadjuvant chemoradiation is administered is about 91%- 100%, and a five year disease free survival rate of 85.4% (39)(40)(41)(42).Downstaging of tumors was also possible in about 81% of patients, when pre-operative chemoradiation was used (43).

As neoadjuvant therapy improves the surgical outcome and has an impact on the survival rates, it is imperative to identify the patients who will benefit from neoadjuvant therapy preoperatively. Hence, the role of imaging in accurate staging of rectal cancer in the initial staging examination is important.

Local recurrence following the treatment in rectal cancer is a worrisome occurrence. The various factors leading to bad outcome are (44).

- the histological grade of tumor

- histopathological type of tumor

- the extent of extra-mural spread of tumor

- invasion of venous or lymphatic channels

- configuration of tumor border

- tumor budding

- lymphoid response of the host

Imaging in carcinoma rectum:

With the introduction of 3- Tesla MRI, the local staging of rectal tumors has become more accurate (45).

T2 high resolution imaging MRI images can accurately identify (46)

- the local stage of rectal cancer

- extramural depth of tumor invasion

- nodal involvement

- circumferential resection margin

- presence of extramural vascular invasion

All the above parameters have been known to affect the prognosis in rectal cancer and by identifying these, the feasibility of surgery, and the need for neoadjuvant therapy can be assessed.

The stage at presentation, involvement of mesorectum and presence of mesorectal nodes play a crucial role in determining the suitable management.

Hence, staging in MRI examination should identify (47)

- patients with extramural spread of tumor who may require neoadjuvant therapy

- patients with no involvement of the anal sphincter complex who may be able to have a sphincter sparing surgery

The identification of accurate staging is important in devising the treatment plan, deciding the surgical approach and determining the prognosis.

Interpretation of MRI imaging:

The anatomy of the rectal wall is clearly delineated in the high resolution magnetic resonance imaging. The submucosal and mucosal layer are seen as an inner hyperintense layer, the muscularis propria as middle hypointense layer and the outer perirectal fat tissue as hyperintense layer (20). The mesorectal fascia surrounds the rectum and mesorectum which contains fat tissue, lymph nodes and vessels. Superiorly, the mesorectal fascia merges with the peritoneal reflection. The pelvic peritoneal reflection is seen in the anterior aspect of rectum and then reflects off the urinary bladder.

Assessment of tumor characteristics:

A pneumonic “DISTANCE” was coined by Gina Brown et al;, to enable a systematic approach in the reporting of rectal cancers which included the assessment of the following parameters (48).

DIS- Distance from the transitional zone in the anal canal to the inferior margin of the tumor

T – T staging

A – anal sphincter complex

N – Nodal staging

C – CRM/ circumferential resection margin

E – extramural vascular invasion

A guide for synoptic reporting in MRI for rectal cancers for the Canadian cancer society was published in October 2011; which incorporated the findings from multiple studies and attempted to form uniform guidelines in reporting (49).

a) Tumor morphology

i) Tumor location

Depending on the distance from the lower part of tumor to the anal verge, rectal malignancies can be classified into upper, mid and low rectal cancers (48). This is important as the site of tumor influences the type of surgery and also, the outcome (48).

1. Upper rectal cancers: The distance from the anal verge to the lower edge of the tumor is more than 10cm. Anteriorly, pelvic peritoneal reflection surrounds the rectum and hence this can be injured during surgery causing tumor spill.

2. Middle rectal cancers: The distance from the anal verge to the lower edge of the tumor is in between 5 to 10cm. As mesorectum surrounds the middle part of rectum, total mesorectal excision is possible in these tumors and hence, the local recurrence rates will be low.
3. Lower rectal cancers: The lower edge of the tumor is located <5cm from the anal verge. The mesorectum tapers at this level. Hence, the involvement of circumferential resection margin is high. Also, inferiorly, the tumor can involve the anal sphincter complex; which, if present can change the management.

Involvement of anal sphincter complex in low rectal tumors:

If the tumor is above the puborectalis sling, sphincter sparing surgery is feasible; whereas, if the tumor extends below the insertion of levatorani; the patients may need to undergo abdominoperineal excision with a diversion colostomy (49).

ii)Tumor signal intensity:

1. High signal intensity: Tumors with marked high signal intensity on T2 weighted images (isointense to fat or hyperintense to fat). Marked high signal intensity is usually seen in mucinous tumors, which are associated with bad prognosis. The high signal intensity is due to the component of mucin. About 75% of mucinous tumors show high signal. Patients with mucinous tumors detected on MRI had significantly worse three year survival outcome and had a disease free survival

rate of 48% compared to 71% in non-mucinous tumors. Also, MRI detected mucinous tumor was an independent variable in predicting poor disease free survival (29)(50)(51)(52).

2. Intermediate signal intensity: Tumors with signal intensity between muscle and fat. Most of the rectal tumors have intermediate signal intensity.
3. Low signal intensity: Tumors with low signal intensity (equal to muscle)

iii)Type of tumor:(53)

- Circumferential tumors: tumors with circumferential involvement of rectum
- Hemicircumferential tumors: tumors with semi-annular involvement of rectum
- Polypoidal tumors: tumors seen as a polypoidal mass projecting into the lumen.

iv) T staging: (as per AJCC 7th edition)

The T-stage of the tumor indicates the extent of invasion of the rectal wall by the tumor (54)(55)(56)(57)(8).

- **T0 –** no primary tumor is evident
- **T1 -** tumor invades the mucosal and submucosal layer and is replaced by abnormal tumor signal intensity; the muscularis layer is spared
- **T2**– tumor invades muscularispropria layer; but does not extend beyond muscularis layer and is characterized by abnormal tumor signal intensity.

- **T3-** tumor extend beyond the muscularis propria to involve the mesorectal fat. The thin hypointense line between the muscularis layer and mesorectal fat is usually lost.

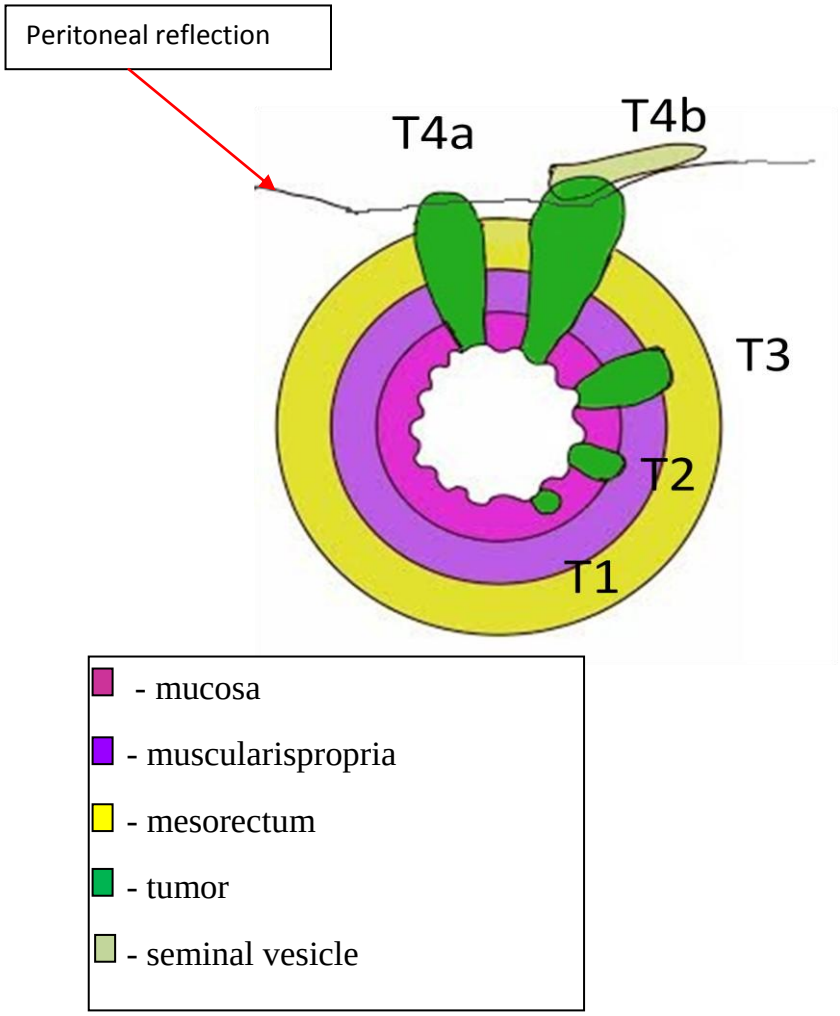
  The T3 stage is further classified intofour groups. This is mainly to identify the extent of extramural spread of tumor. Many studies have shown increased rates of local recurrence and poor survival rates in tumors with extramural spread beyond 5mm (25)(58).

  - T3a– Tumour extends <1mm beyond the muscularis layer
  - T3b - Tumour extends >1-5 mm beyond the muscularis layer
  - T3c - Tumour extends > 5-15 mm beyond the muscularis layer
  - T3c - Tumour extends >15 mm beyond the muscularis layer
- **T4-** tumors invades the surrounding organs and peritoneum
  - T4a – Tumor involves visceral peritoneal surface
  - T4b – Tumor involves adjacent organs or structures

Patients with T3 and T4 disease with nodal disease and involved circumferential resection margin will require multimodality therapy.

Studies have shown that high resolution MR imaging is good in accurately identifying the "T" stage of tumor preoperatively (46) There was good agreement between the "T" stage on high resolution MRimaging and that on pathological T staging (weighted kappa of = 0.67) (46).

Diagrammatic representation of T staging of carcinoma rectum:



T1 - tumor invading mucosa

T2 –tumor invading mucosa and muscularis layer

T3 – tumor with extramural spread

T4a- tumor involving peritoneum

T4b- tumor involving adjacent structures

Anal sphincter complex:

Anal canal is the distal most part of alimentary tract and extends from the anorectal junction at the level of puborectalis sling superiorly and anal verge inferiorly. The anal sphincter complex consists of internal and external anal sphincters, which can be clearly

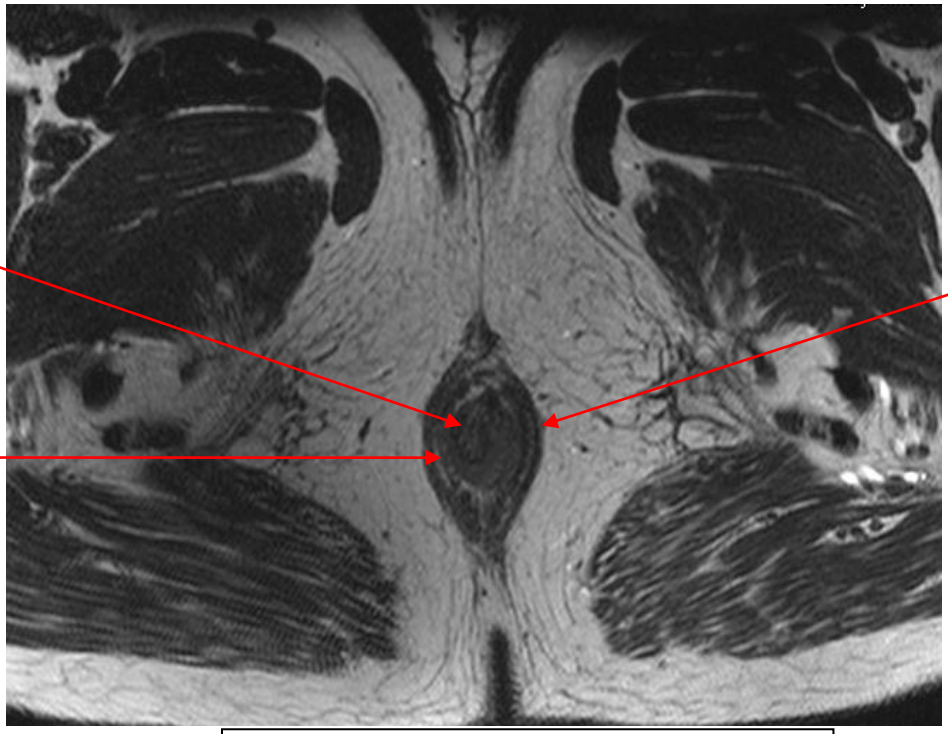
visualized on high resolution MR images. The low rectal malignancies can extend inferiorly and involve the anal sphincter complex. Sphincter saving surgery may not be possible if anal sphincters are infiltrated and patient may require colostomy. Hence the identification of anal sphincters and assessment of infiltration of sphincters by the tumor is important (59)(21).

Imaging appearance of anal sphincter complex on MRI:

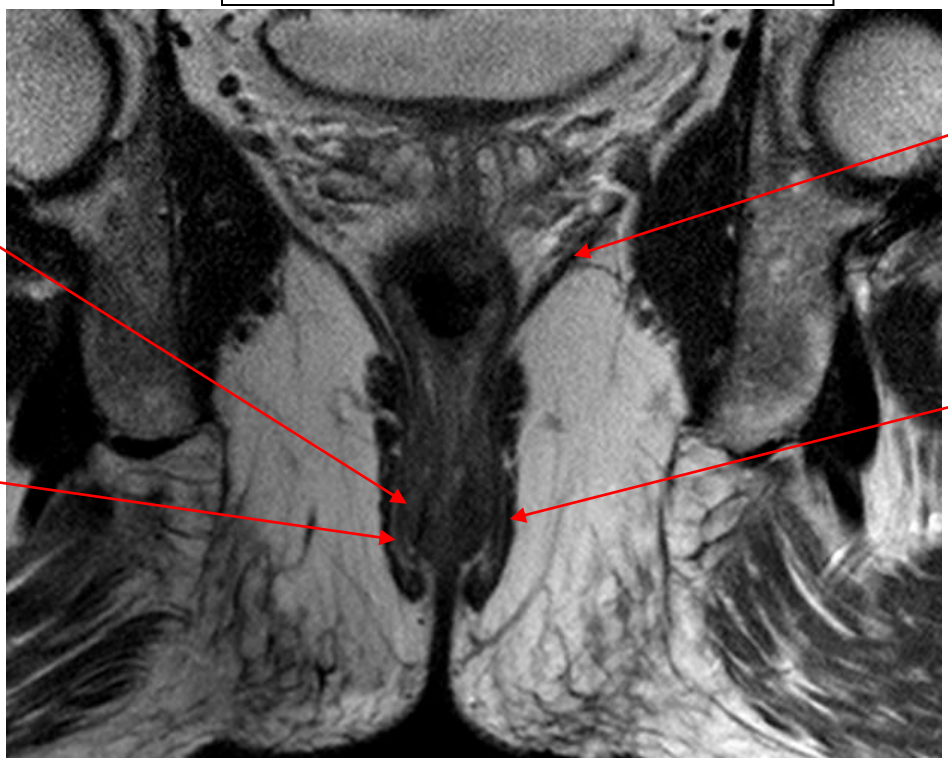
The external anal sphincter appears hypointense on T2 weighted MR images; whereas the internal anal sphincter appears to be of intermediate signal intensity. A thin fat containing space named intersphinteric space separates these two muscles. At the superior margin of external anal sphincter,puborectalis muscle forms a sling around the rectum and gets inserted into the pubic bone (59)(60).

The extent of involvement of the anal sphincter complex should be mentioned in the reporting as this has an impact in the management

T2 HR MRI axial section at the level of anal



T2 HR MRI coronal section at the level of anal



A- internal anal sphincter,

B- external anal sphincter

C- intersphincteric space (hyperintense plane between internal and external anal sphincters)

D- levator ani muscle

Nodal disease:

Patients with nodal disease usually require neoadjuvant therapy to reduce local recurrence rate.

Multiple studies have advocated various cut off for size of mesorectal lymph nodes. To identify the mesorectal nodes involved with tumor, when a cut off of size 6mm is employed, the sensitivity and specificity of MRI is 77.8% and 78.3% respectively (61).When lymph nodes of size ≥8mm are considered as positive, there was good agreement between the pathological and MRI nodal stage (62) The sensitivity and specificity to predict nodal metastasis when the nodes have mixed signal intensity and irregular borders are 85% and 98% respectively (63)(64)(65).

Hence, any mesorectal lymph node with an irregular border, mixed signal intensity and or size ≥ 8mm in the short axis was considered as positive lymph node in this study.

N staging:

- N0 - No regional lymph node metastasis
- N1 – Metastasis to regional nodes , 1-3 in number
  - N1a – Metastasis to 1 regional node
  - N1b- Metastasis to 2 to 3 regional nodes
  - N1c – Tumor deposits in the subserosa, mesentery or non-peritonealised pericolic or perirectal tissues with no metastasis to regional nodes

- N2 – Metastasis in regional nodes , 4 or more in number
  - N2a – Metastasis to regional nodes, 4 to 6 in number
  - N2b – Metastasis to regional nodes, 7 or more

M staging: (as per AJCC 7th edition)

M0 – No distant metastasis

M1 – Presence of distant metastasis

- M1a – metastasis to one organ or site
- M1b – metastasis to more than one site or organ or to the peritoneum

TNM stage of tumor:

The TNM staging as per AJCC 7th edition is as given below:(66)

Stage	T	N	M
0	Tis	N0	M0
I	T1/T2	N0	M0
IIa	T3	N0	M0
IIb	T4a	N0	M0
IIc	T4b	N0	M0
IIIa	T1,T2	N1/N1c	M0
	T1	N2a	M0
IIIb	T3,T4a	N1/N1c	M0
	T2,T3	N2a	M0
	T1,T2	N2b	M0
IIIc	T4a	N2a	M0
	T3,T4a	N2b	M0
	T4b	N1 or N2	M0
IVa	Any T stage	Any N stage	M1a

In stage I-III disease, after R0 resection, about 10% tumors developed at upper rectum, 8% at mid rectum and 6% at low rectum. However, the rates of local recurrence significantly reduced after administration of neoadjuvant therapy (67).

Circumferential Resection Margin (CRM):

The rectum and perirectal fat tissue is surrounded by mesorectal fascia which is seen as a thin hypointense line on T2 weighted MR images. It gradually tapers when it reaches the lower rectum (64). Fat tissue, lymph nodes and vessels are seen in the mesorectum.

Circumferential resection margin is the shortest distance between the tumor and mesorectal fascia and is expressed as millimeter. It is an important prognostic indicator in rectal cancer in determining tumor recurrence (68). A CRM of less than 1mm was associated with local recurrence while those patients with a CRM of less than 2mm had distal recurrence (31).

A CRM of less than 2mm was considered as positive in our study.

Extramural Vascular Invasion (EMVI):

The presence of malignant cells in the blood vessels in the mesorectum indicates extramural vascular invasion. It is seen in about 10-22% of patient after surgery and is considered to be an important indicator in assessing the prognosis in rectal cancer. EMVI is classified as positive or negative based on the presence of extramural vascular invasion. Vessels are seen as serpiginous structures in the mesorectum which are identified in serial sequences (49)

Brown et al; has proposed a classification based on MRI, which has a sensitivity of 62% and specificity of 88%. Also, there was fair to moderate agreement between radiologists while using this classification (weighted kappa of 0.41) (20).

EMVI positive:(49)(8)

- Intermediate signal intensity in the blood vessels adjacent to the tumor or

- Irregular vessel contour (vessel expanded by tumor)

EMVI negative:

- When the tumor extending through the muscularis layer is not nodular, or the tumor does not extend adjacent to vessels

- Normal caliber vessels with no tumor signal, when is stranding adjacent to vessels

Patients with positive extramural vascular invasion were found to have advanced T stage, nodal disease on histology and also had more distant metastases. Also, the three year disease free survival rate was 35% compared with 74% in patients with no or early EMVI. Hence, it an independent prognostic factor causing adverse outcome in rectal cancer and needs to be carefully looked for, in the pre-operative imaging (8)(57)(69).

Re-staging of locally advanced rectal cancer on MRI after neoadjuvant therapy:

The follow up imaging after neoadjuvant therapy in rectal cancer is aimed at

- restaging the tumor
- assessing the degree of response and plan further treatment
- assessing feasibility of surgery

Parameters used for assessment in re-staging MRI:

Patel et al; has advocated the assessment of following parameters while restaging rectal cancer. High resolution images are used to assess these factors (8)(9).

- Appearance of the tumor (includes presence of mucinous / necrotic / fibrosis component)
- Distance between the lower edge of tumor and anal verge (this should be compared with pre-therapy imaging)
- Length of the rectal tumor (this should be compared with pre-therapy imaging)
- MRI tumor regression grade
- Depth of extramural invasion by the tumor
- T stage (including substage) on MRI

- Involvement of CRM

- Presence of EMVI

- N staging (presence of pelvic sidewall lymph nodes has to be mentioned)

- Involvement of pelvic peritoneal reflection

Apart from this, a few other factors should be mentioned including:

- Involvement of anal sphincter complex in low rectal tumors which are located below the insertion of levator ani.

- Diffusion restriction in the residual tumor, when diffusion weighted imaging is available.

i) Appearance of tumor:

The tumors which showed intermediate signal can show areas of high signal following neoadjuvant therapy (colloid response). This is due to necrosis and subsequent mucinous degeneration. The rate of local recurrence in the subset of patients who showed colloid response is not known to show any significant difference from other patients (70)(71).

Areas of high signal representing acellular mucin pools are also seen in mucinous tumors. Studies have shown favorable outcome in tumors with presence of mucin pools (72).

ii) T, N and M staging:

MRI is less sensitive in identifying T stage and nodal stage following neoadjuvant therapy. MRI examination shows an accuracy of about 45-54%, in predicting the T stage, after the neoadjuvant treatment compared to 71-91% accuracy in pre-therapy imaging. However, the accuracy in predicting nodal stage in restaging MR examination is similar to pre-therapy imaging (64% to 68% compared to 43%-85% in prê-therapy MRI) (73)(74)(75).

Problems in staging occur due to presence of fibrosis which is seen as hypointensity on MRI images, making it difficult to distinguish with the primary tumor.

Overstaging of MRI T stage can occur in 33-38% of patients and that of N stage in about

4%. Understaging can also occur 20-22% of MRI T stage and 19% of N stage. The overall accuracy of MRI in staging of post therapy rectal tumors is about 43% (73)(76)(77).

iii) Involvement of CRM:

The accuracy of post –therapy MRI examination in predicting the involvement of CRM is about 66-81%; with a sensitivity of 100 % and specificity of 35% (73).

Hence MRI is useful in assessing parameters like CRM and EMVI which has a significant association with the outcome and further treatment plan.

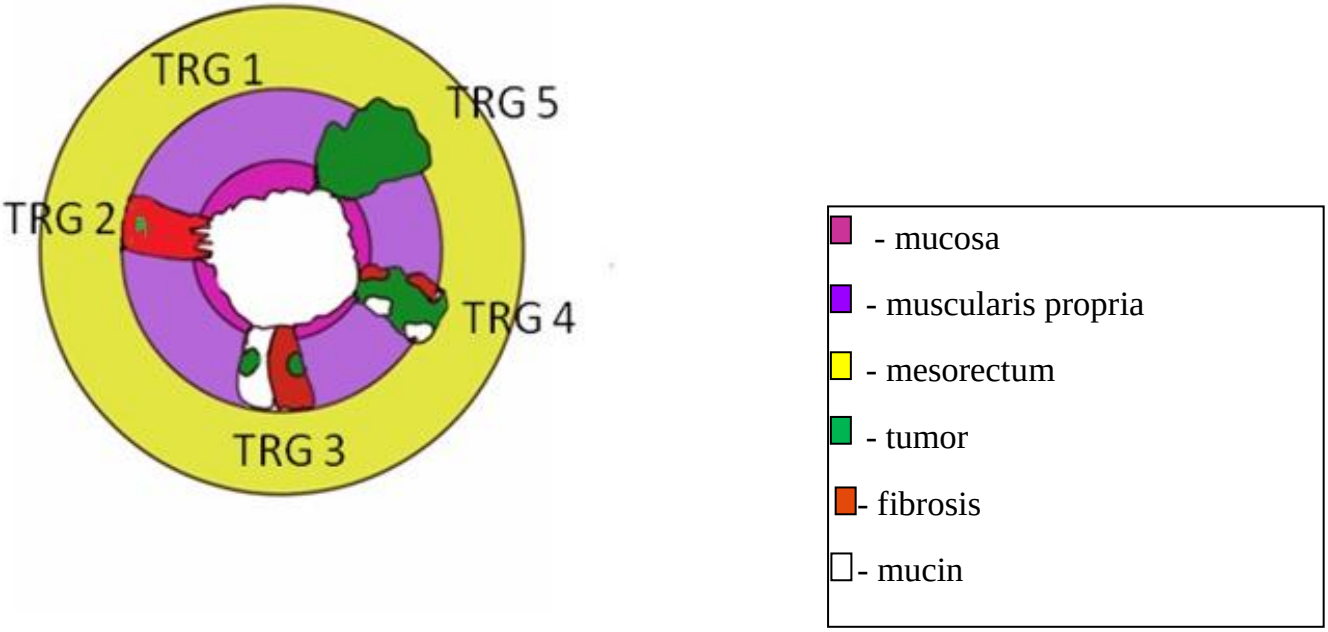
MRI Tumor Regression Grading (proposed by MERCURY) - TRG

MERCURY study conducted in 2002 assessed the accuracy of MRI in assessing the extent of the extramural depth of invasion by the tumor in patients diagnosed with rectal cancer (9). Using the data from this study, MRI tumor regression grading was designed to reflect the pathological tumor regression grading system (8). MERCURY study group conducted another study which aimed to assess the response to neoadjuvant therapy in rectal cancer by assessing the MRI tumor regression grading and CRM status concluded that MRI assessment of tumor regression grading and CRM status predict survival outcome and also aids in planning further treatment before surgery (9).

MRI tumor regression grading:(9)

Grade 1	complete response on MRI imaging; no evidence of tumor
Grade 2	the response is good; only minimal residual disease; dense fibrosis is seen
Grade 3	the response is moderate; visible intermediate tumor signal; however, more than 50% is mucin and fibrosis
Grade 4	the response is mild; mostly tumor is seen; few areas of mucin or fibrosis
Grade 5	the response is nil; no change from the baseline tumor signal

Diagrammatic representation of MRI tumor regression grading



Patients with a TRG of 4 and 5 respond poorly to treatment and has worse long term outcomes(78). Study conducted by Patel et al had shown decreased five year survival rate (27%) and disease free survival (31%) in patients with poor MRI TRG (TRG 4 and TRG 5) compared to patients with good TRG (TRG 1,2 and 3) (9).

Low rectal tumors with poor TRG on MRI (TRG 4 and 5) has increased rate of disease recurrence and death (79).

Newer techniques in MRI imaging:

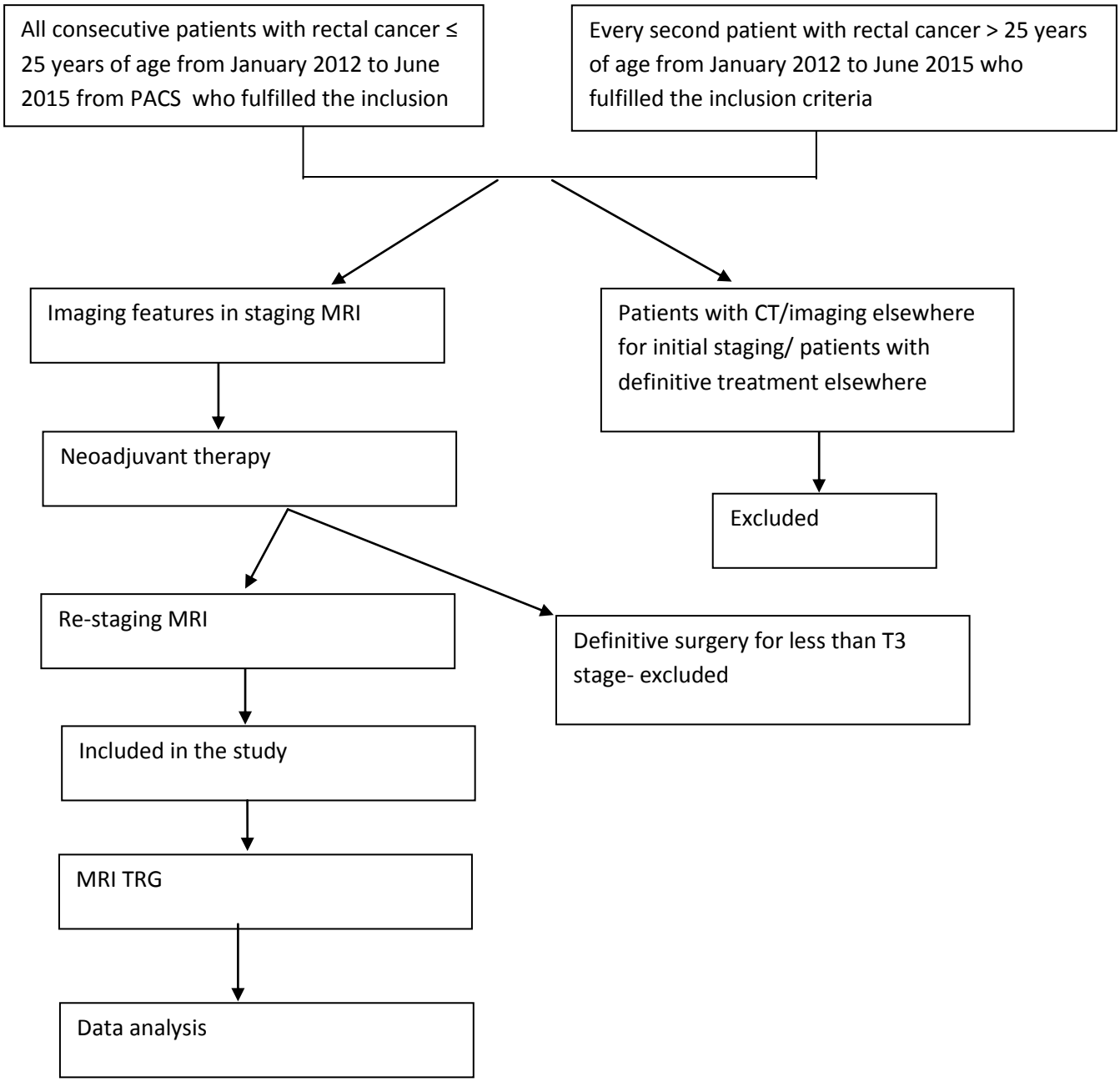
Diffusion weighted imaging is a newer technique, which further helps in identifying the accurate local stage and nodal disease in rectal carcinoma. When it is used as complementary to T2 weighted MR imaging, the sensitivity and specificity in identifying rectal tumors is about 93-95% and 95-100 % respectively (80)(81).

ANALYSIS AND RESULTS:

A) Study design: Observational study

Duration of study: This was a partly retrospective andpartly prospective study and was carried out from January 2012 to June 2015.

Sample size: A total of 142 patients were included in the study.



The data was analysed after the patients were divided into older and younger age groups; that is ≤25 years of age and >25 years of age.

B) Patient demographics:

a) Age distribution:

Age	Number	Percentage
≤25 years	27	19
>25 years	115	81

Around 27 young patients (≤ 25 years of age) fulfilling the criteria were included in the study. Out of 231 older patients (>25 years of age) fulfilling the criteria, 115 patients were included in the study.

b) Mean age at presentation:

Age group	Mean age
≤ 25 years	22
> 25 years	46

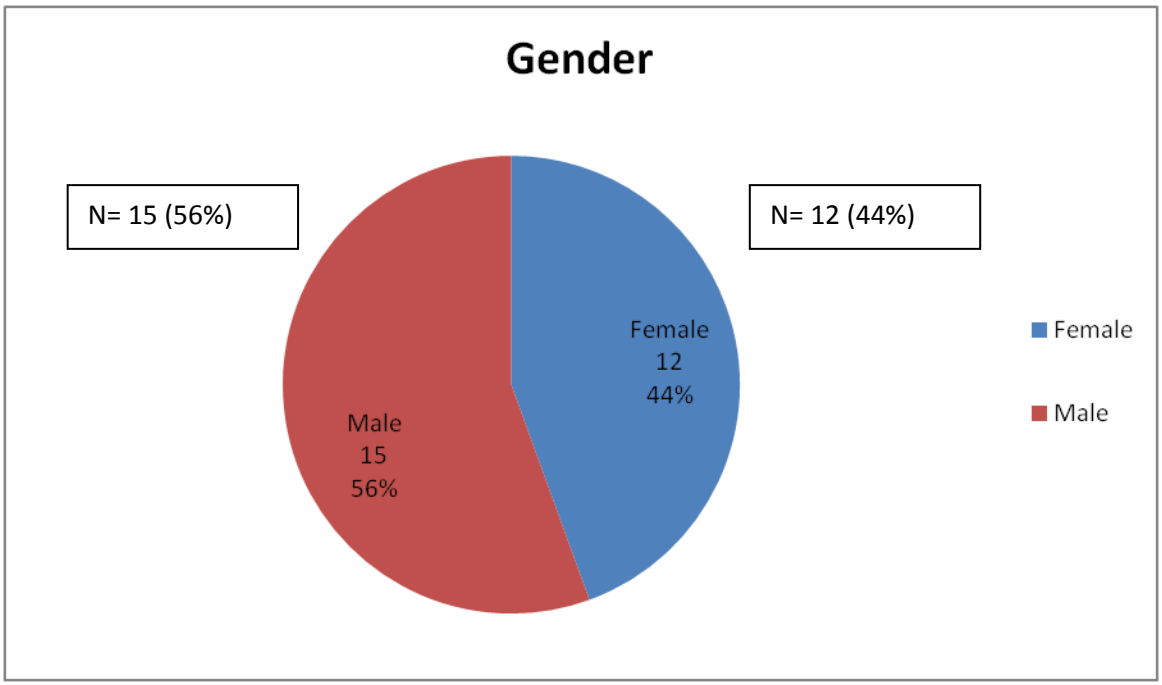
b) Gender distribution:

Among the 142 patients included in the study,

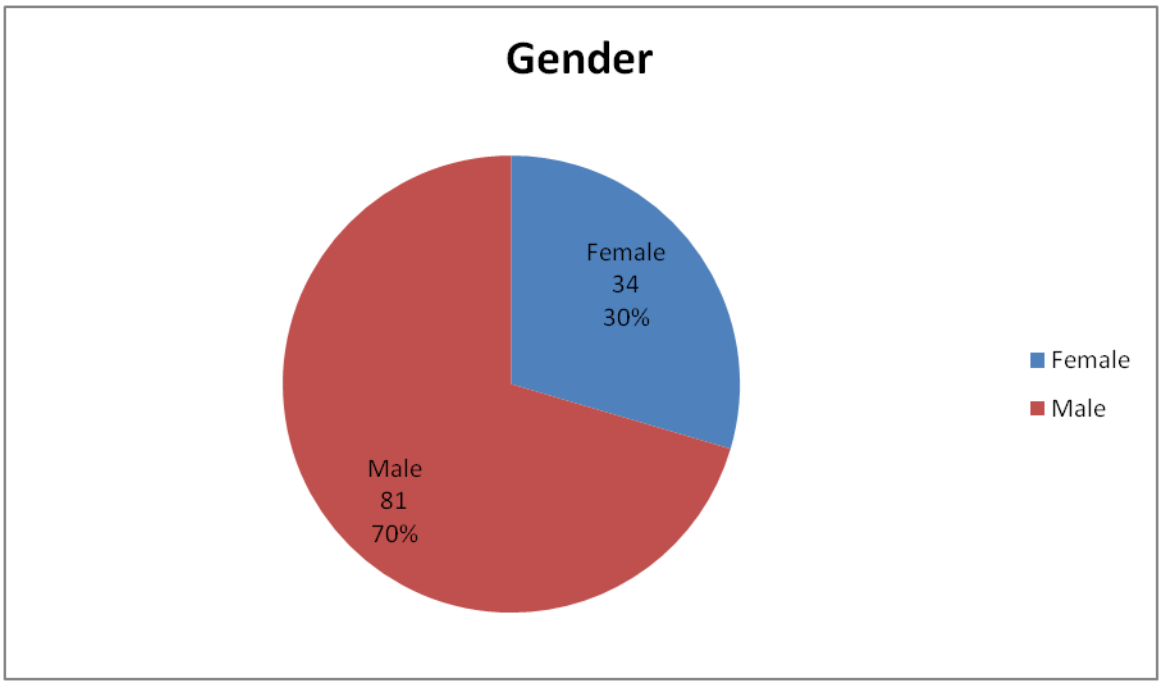
- 46 patients (32.4%) were women.

- 96 patients (67.6%) were men.

i) In the younger age group (≤ 25 years of age)



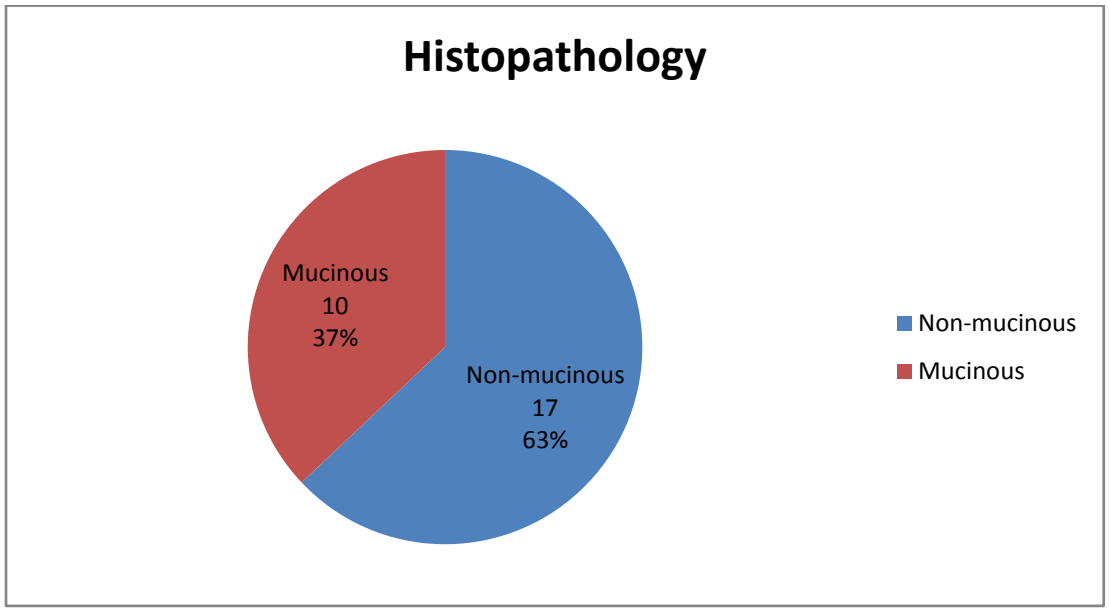
ii) In the older age group (> 25 years of age)



C) Tumor histopathology:

i) Histological type in the younger age group (≤ 25 years of age)

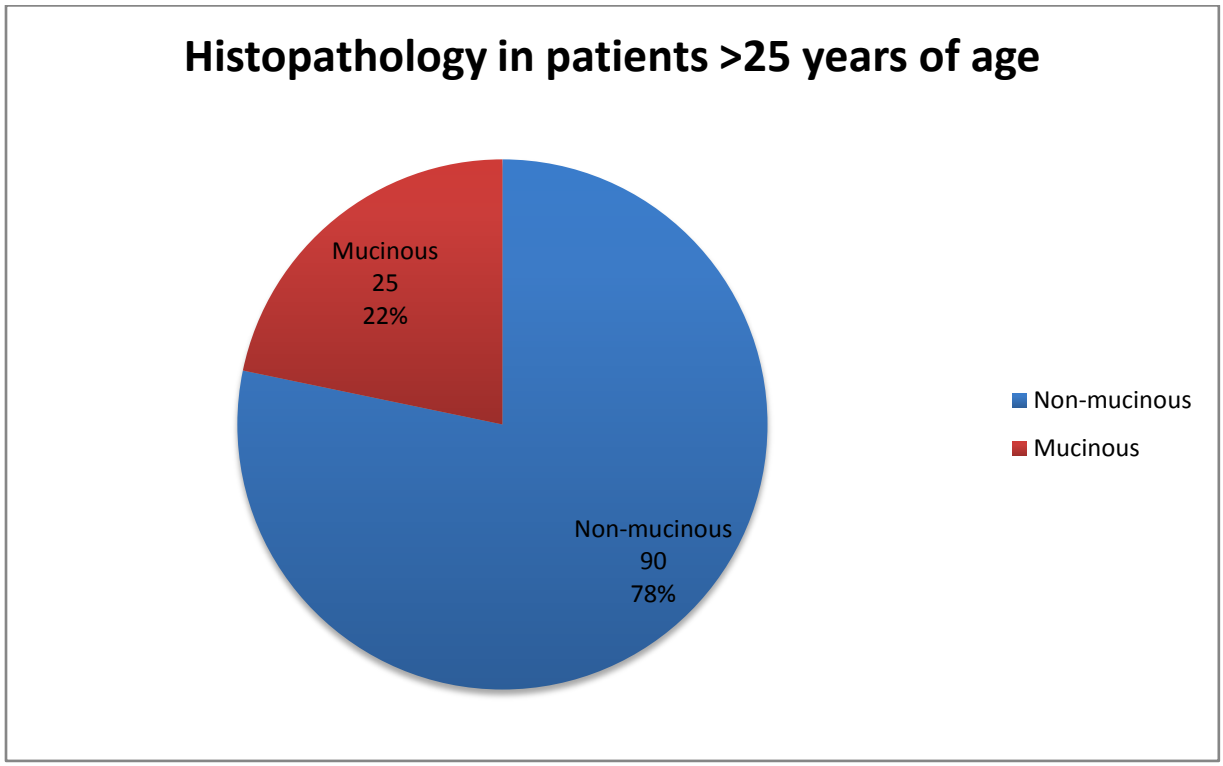
Histopathology	Non-mucinous adenocarcinoma	Mucinous adenocarcinoma	Signet ring cell carcinoma
Number (n)	17	3	7
Percentage(%)	63	11.1	25.9



Among younger age group, 37% were mucinous cancers and around 26% of these were signet ring cell carcinomas.

ii) Histological type in the older age group (> 25 years of age)

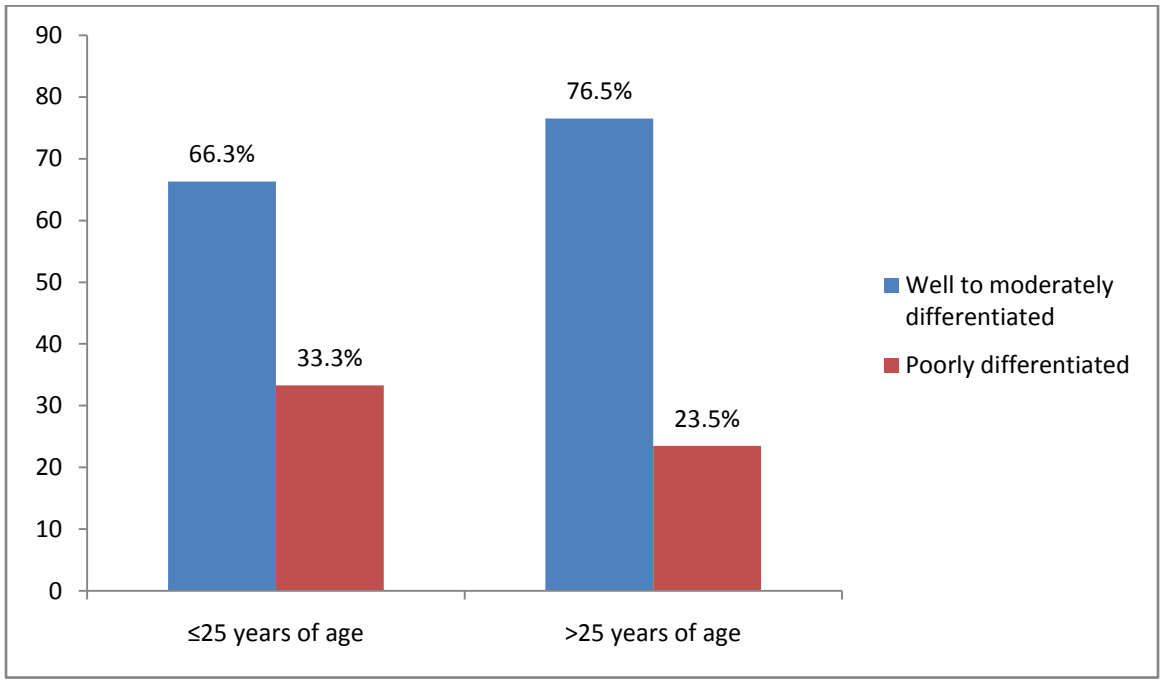
Histopathology	Non-mucinous adenocarcinoma	Mucinous adenocarcinoma	Signet ring cell carcinoma
Number (n)	90	8	17
Percentage(%)	78.3	7	14.8



iii) Tumor histopathological grading

	Well differentiated	Moderately differentiated	Poorly differentiated	Total number
≤25 years of age	1 (3.7%)	15 (55.6%)	9 (33.3%)	25
>25 years of age	3 (2.6%)	73 (63.5%)	27 (23.5%)	103

Histopathological grading:



D) Details of treatment:

i) Type of neoadjuvant therapy:

	Short course radiation	Long course chemoraditaion	Radical chemoradiation	Chemotherapy alone	Total number
≤25 years of age	0 (0%)	23 (85.2%)	0 (0%)	4 (14.8%)	27
>25 years of age	1(0.9%)	103 (89.6%)	2 (1.7%)	9 (7.8%)	115

Most of the patients in both age groups (85.2% in young and 89.6% in old patients) received long course chemoradiation.

ii) The following patients had concurrent chemotherapy and radiation therapy as part of radiation therapy:

	Number of patients who had concurrent chemotherapy	Total number of patients
≤25 years of age	23 (85.2%)	27
>25 years of age	105(91.3%)	115

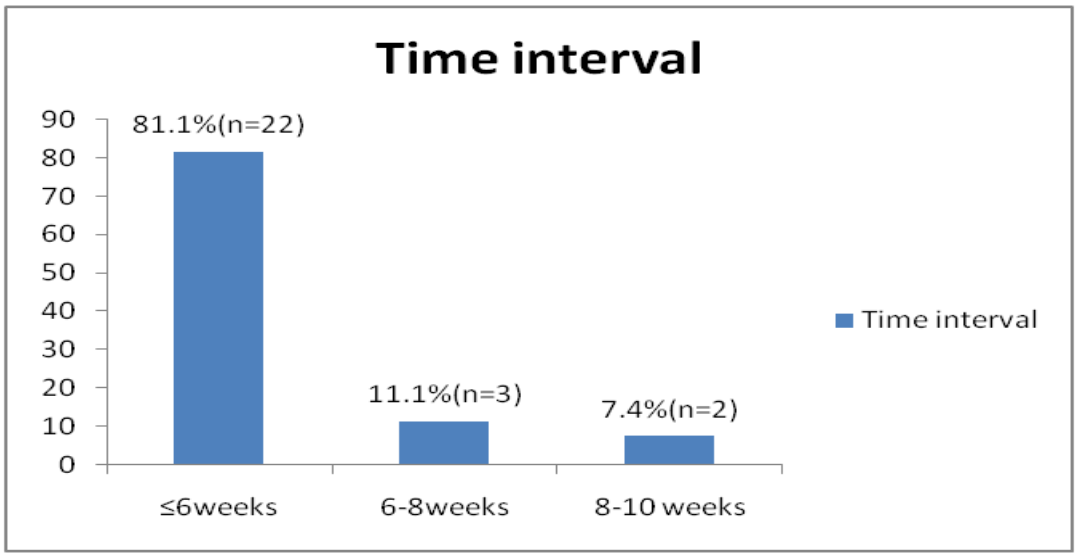
Most of the patients in both age groups had received concurrent chemotherapy.

iii) Details of radiation therapy:

All patients who received radiation therapy as part of long course chemoradiation received 5040 Gy in 28 fractions. Two patients received 5400Gy radiation and one patient received 25Gy radiation in 5#.

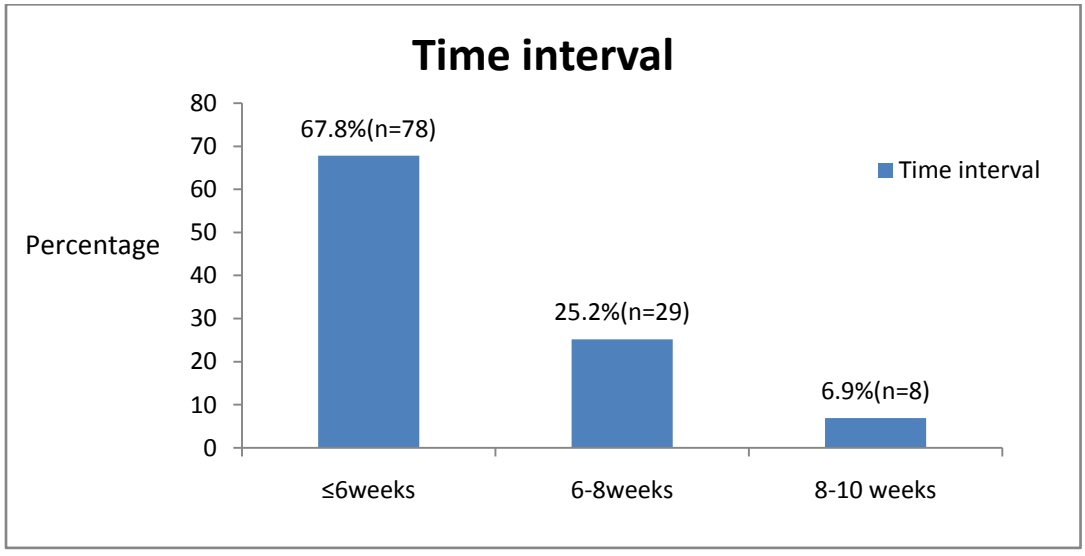
E) Timing between neoadjuvant therapy and re-staging MRI examination

i) In the younger age group (≤25 years of age):



Most of the patients (81.1%) had re-staging MRI within six weeks after the neoadjuvant therapy.

ii) In the older age group (>25 years of age):



About 67.7% of the patients had follow up imaging within six weeks, and 25.2% had re-imaging within eight weeks.

F) Tumor characteristics on initial staging MRI:

a) Tumor location:

i) In the young age group (<25 years of age):

Location	High rectal	Mid rectal	Low rectal	Total number
Number of patients(n)	5 (18.5%)	8 (29.6%)	14(51.9%)	27

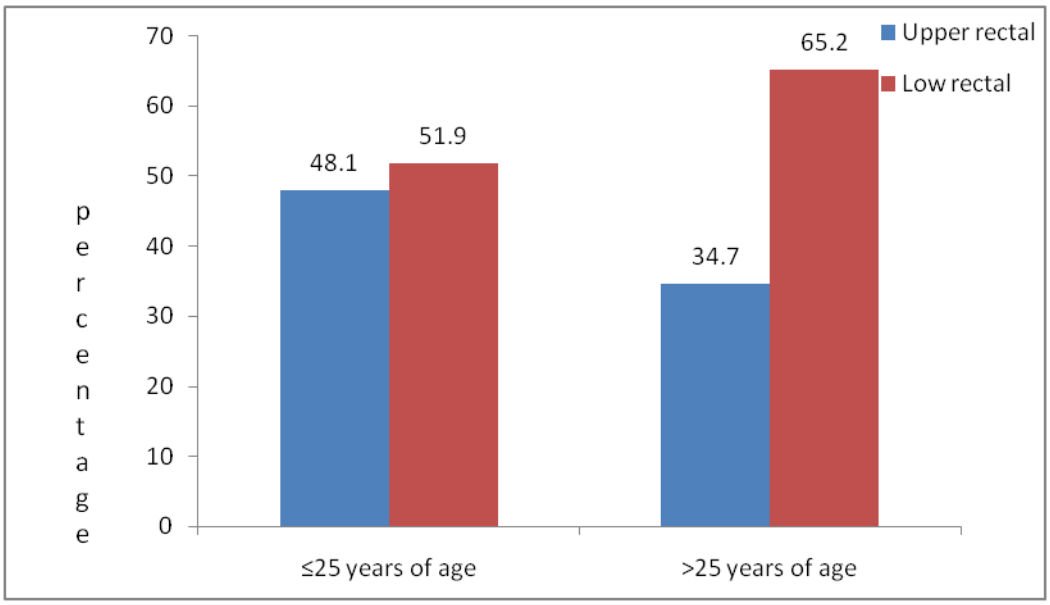
ii) In the older age group (>25 years of age):

Location	High rectal	Mid rectal	Low rectal	Total number
Number of patients(n)	5 (4.3%)	35 (30.4%)	75(65.2%)	115

iii) Comparison between the two groups:

The high and mid rectal tumors are classified as upper rectal and this was compared with the low rectal tumors.

Age versus tumor location:



Most of the tumors in both younger and older age groups were low rectal tumors. About one-third of tumors in both younger and older age groups were in the mid rectum (29.6% in the younger and 30.4% in the older age groups).

- 18.5% of tumors in patients ≤ 25 years of age were upper rectal tumors.

- 4.3% of tumors in patients >25 years of age were in the upper rectum.

Fig:a

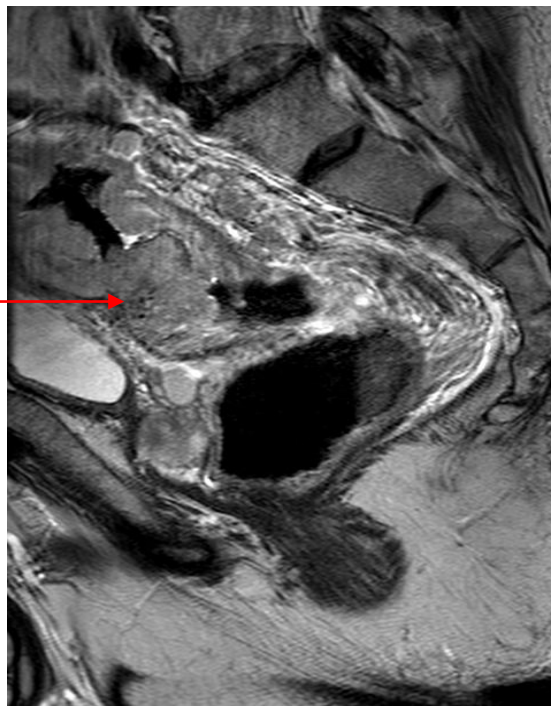
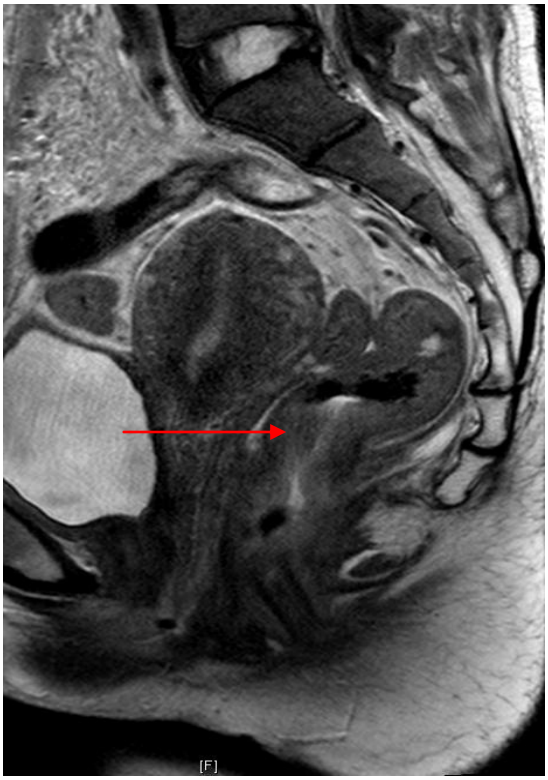


Fig:b

Fig:c



MRI sagittal sections showing

- an intermediate signal intensity tumor in the upper rectum (fig:a)

- a high signal intensity tumor in the mid rectum (fig:b) and

- an intermediate signal intensity tumor in the low rectum (fig:c)

b) Type of tumor:

i) In the younger age group(<25 years of age):

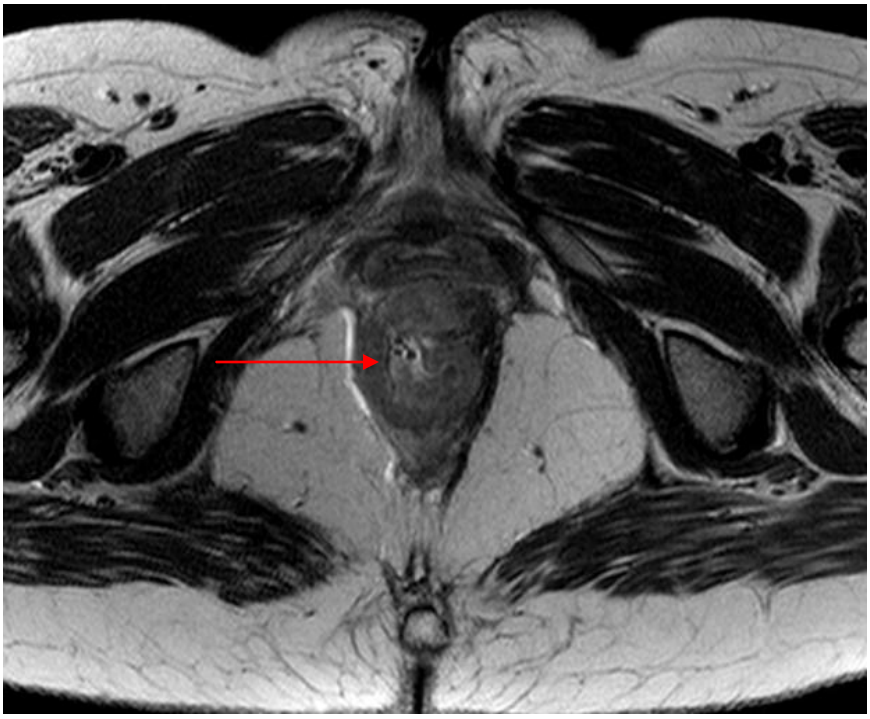
Type	Circumferential	Hemicircumferential	Poylpoidal	Total number
Number of patients(n)	18 (66.7%)	3 (11.1%)	6(22.2%)	27

ii) In the older age group (>25 years of age):

Type	Circumferential	Hemicircumferential	Poylpoidal	Total number
Number of patients(n)	75 (65.2%)	21 (18.3%)	19(16.5%)	115

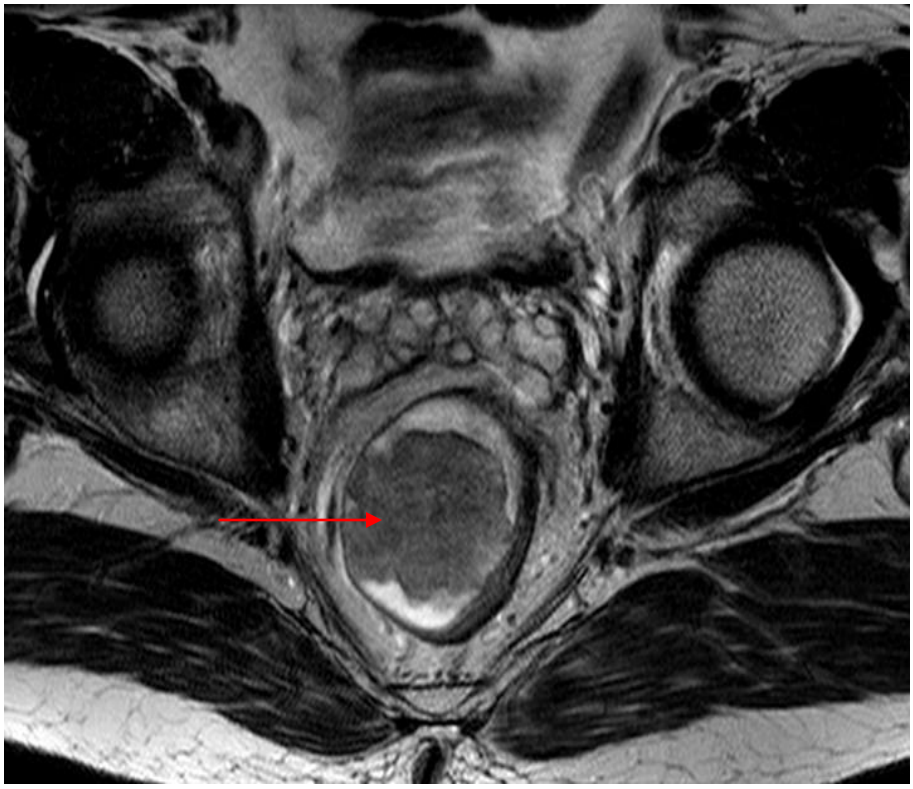
Most of the tumors in both younger and older age group were circumferential growths

(66.7% in the patients ≤ 25 years of age and 65.2% in the patients > 25 years of age)



MRI axial section showing a circumferential rectal tumor with intermediate signal intensity

MRI axial section showing a hemi-circumferential rectal tumor with intermediate signal intensity



MRI axial section showing a polypoidal rectal tumor with intermediate signal intensity

c) T2 signal intensity of tumor:

i) In the younger age group (<25 years of age):

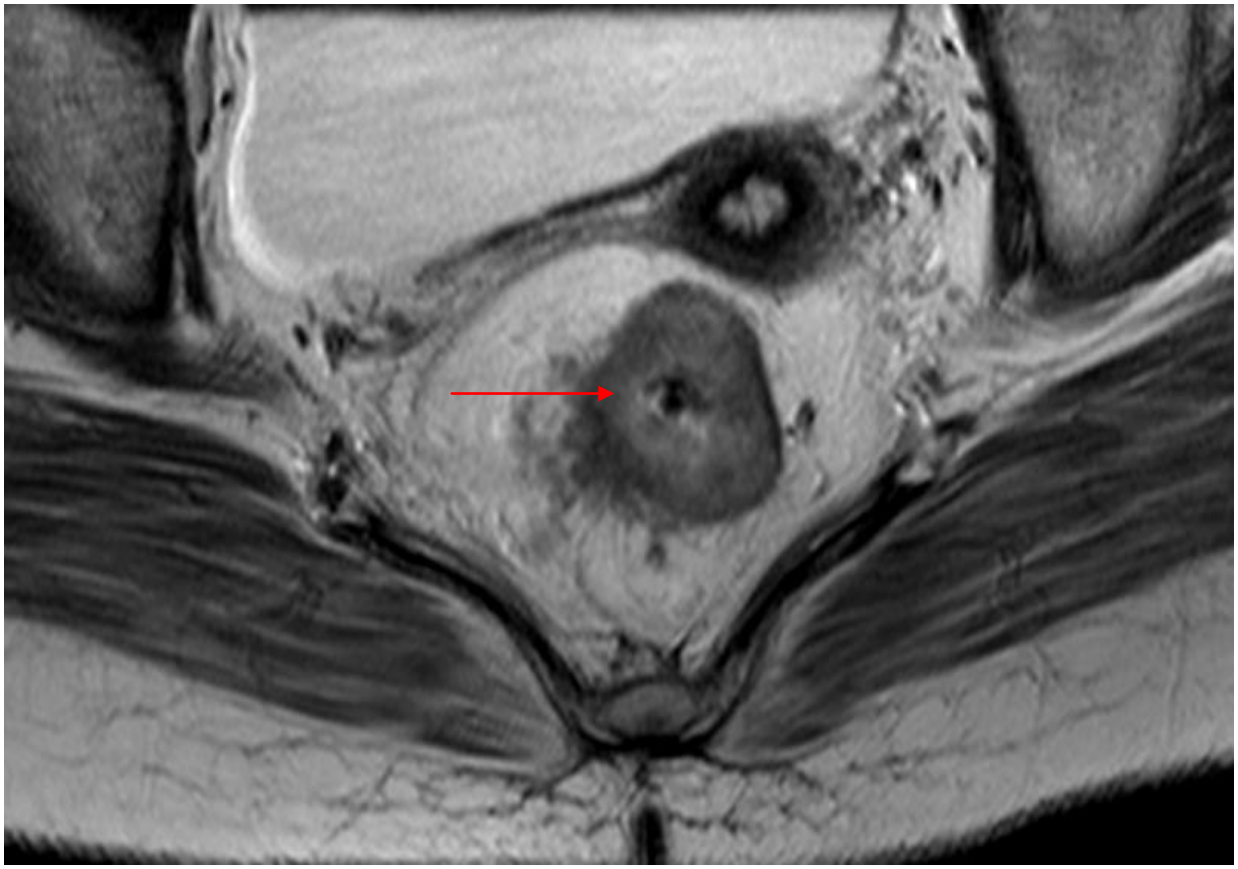
T2 signal intensity	High signal	Intermediate signal	Low signal	Total number
Number of patients(n)	13 (48.1%)	13 (48.1%)	1(3.7%)	27

ii) In the older age group (>25 years of age):

T2 signal intensity	High signal	Intermediate signal	Low signal	Total number
Number of patients(n)	22 (19.1%)	87 (75.7%)	6(5.2%)	115

Most of the patients in the older age group (more than 25 years of age) had tumors with intermediate tumor signal intensity. The percentage of high signal tumors was higher in young age group (48.1%) compared to older age group (19.1%).

MRI sagittal section showing a tumor with high signal intensity in the low rectum



MRI axial section showing a tumor with intermediate signal intensity with extramural invasion into the mesorectum

d) Involvement of anorectal complex in low rectal tumors:

Out of 142 patients, 89 had low rectal tumors (62.6%).

--14 (15.7%) patients belonged to younger age group (<25 years of age)

-- 75 (84.3%) patients belonged to older age group (<25 years of age)

i) Involvement of anal sphincter complex or levator ani:

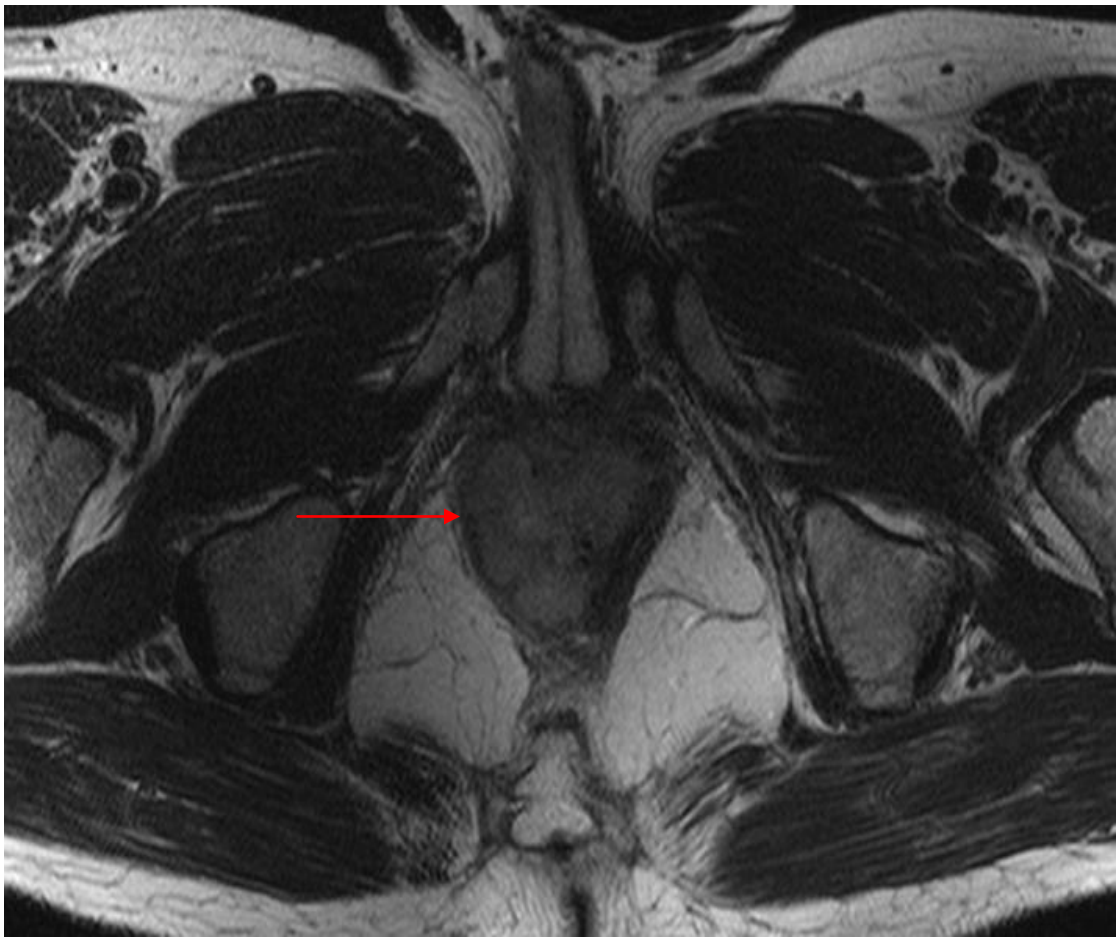
Out of 89 patients with low rectal tumor,

-- 5 patients had external anal sphincter involvement

--31 patients had involvement of internal anal sphincter

-- 29 patients had involvement of levator ani

-- 5 patients had involvement of both internal and external anal sphincters



MRI axial section of pelvis showing an intermediate signal low rectal tumor with infiltration of anal sphincter complex on the right side

e) T stage of tumor:

i) In the younger age group (≤25 years of age):

T stage	T2	T3	T4	Total number
Number of patients(n)	1 (3.7%)	17 (63%)	9(33.3%)	27

ii) In the older age group (>25 years of age):

T stage	T2	T3	T4	Total number
Number of patients(n)	6 (5.2%)	80 (69.6%)	29(25.2%)	115

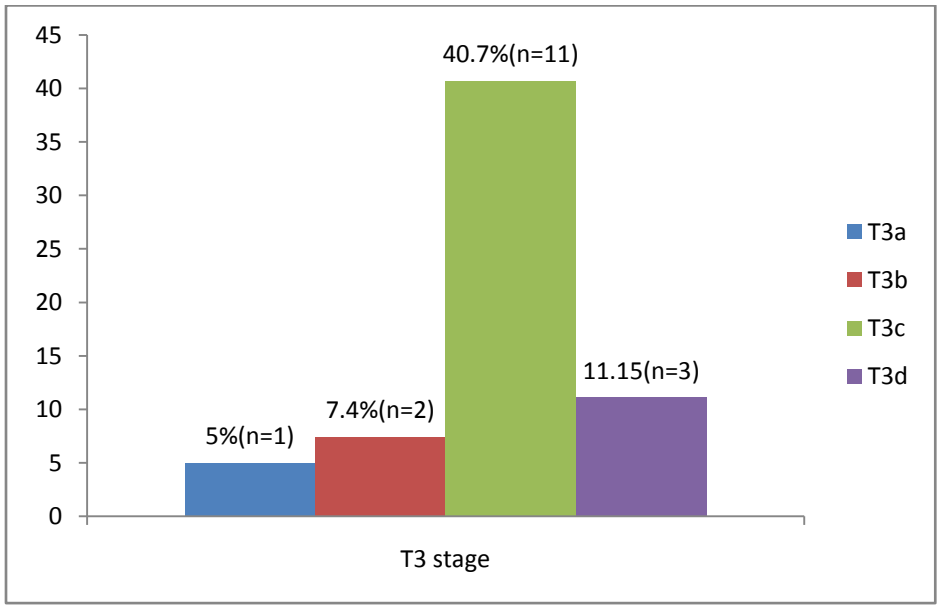
Most of the patients in both younger and older age groups had T3 stage disease.

f) T3 stage of disease:

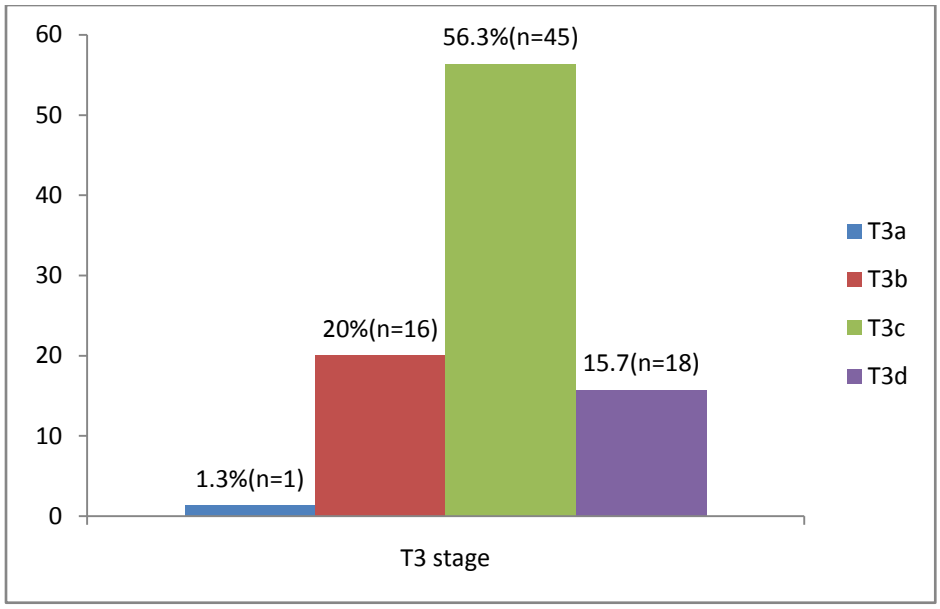
- 17 patients, out of 27patients ≤25 years of age had T3 stage disease.

- 80 patients out of 115 patients >25 years of age had T3 stage disease

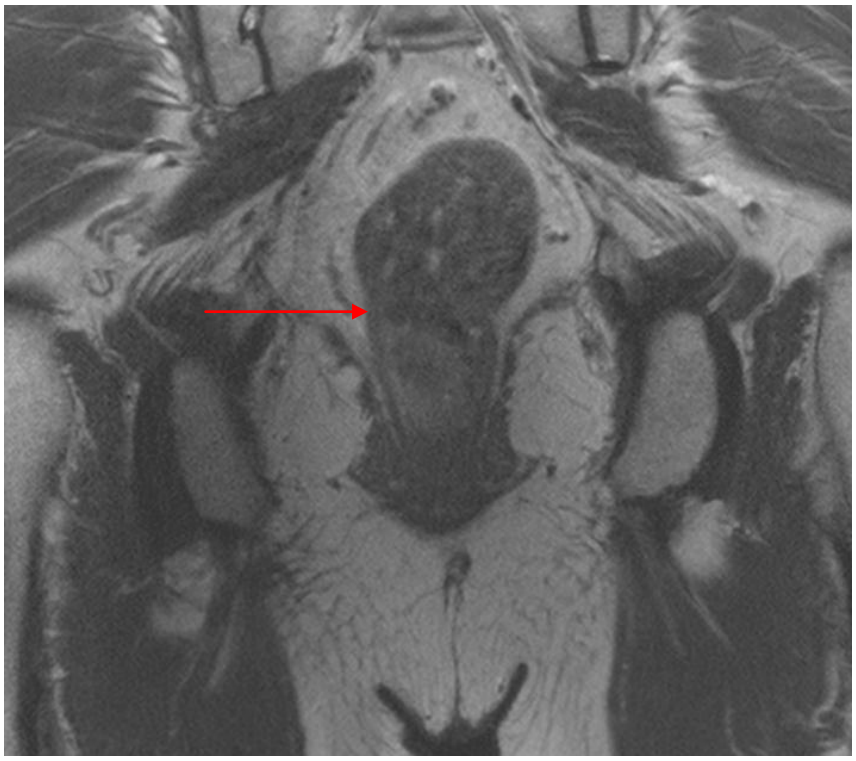
i) In the younger age group (≤25 years of age):



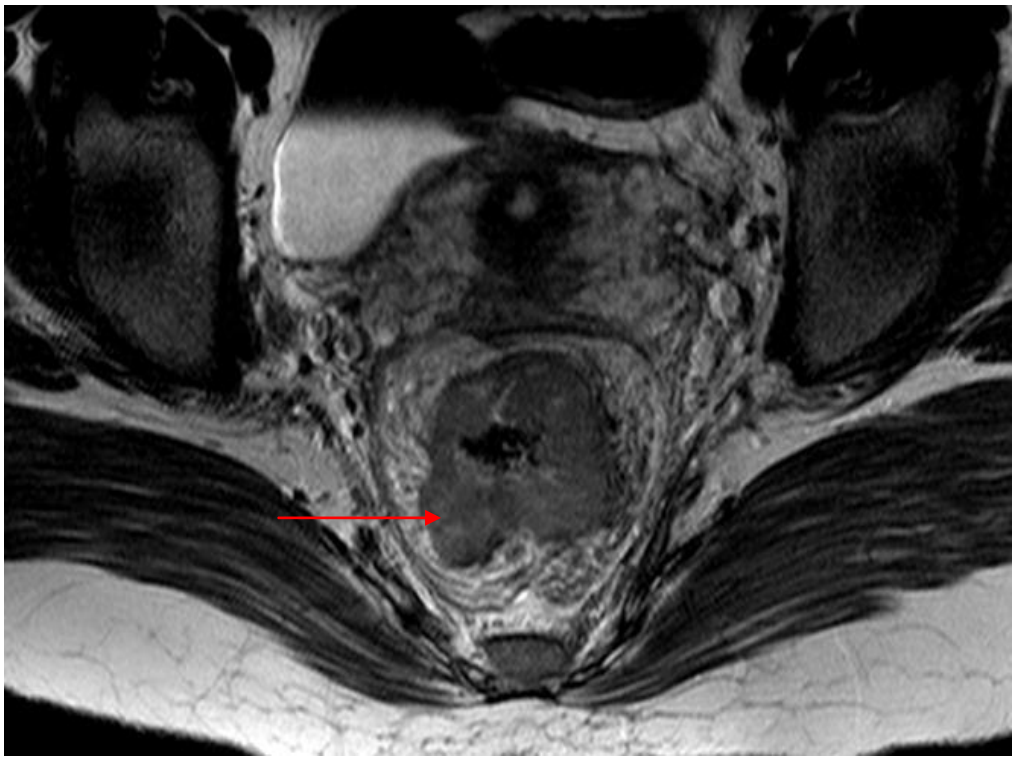
ii) In the older age group (>25 years of age):



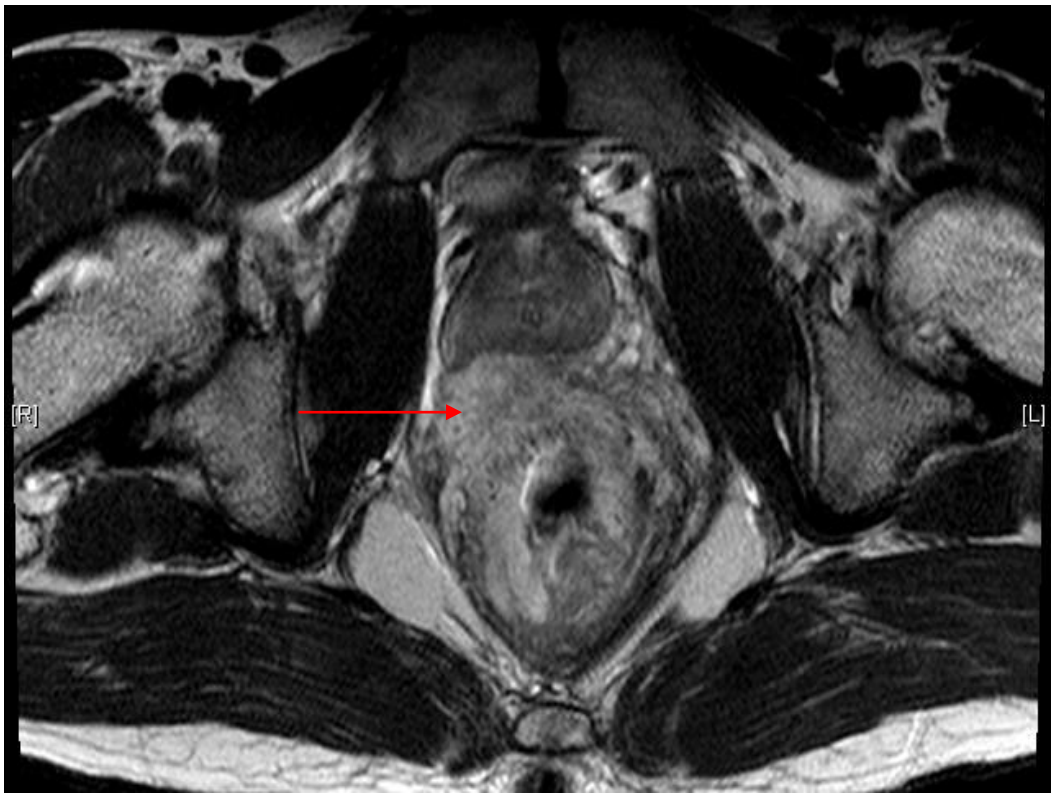
Most of the patients in both younger (40.7%) and older (56.3%) age groups had T3c disease.



MRI axial section of pelvis showing an intermediate signal rectal tumor confined to rectal wall- T2 disease



MRI axial section of pelvis showing an intermediate signal rectal tumor with extramurl invasion – T3 disease

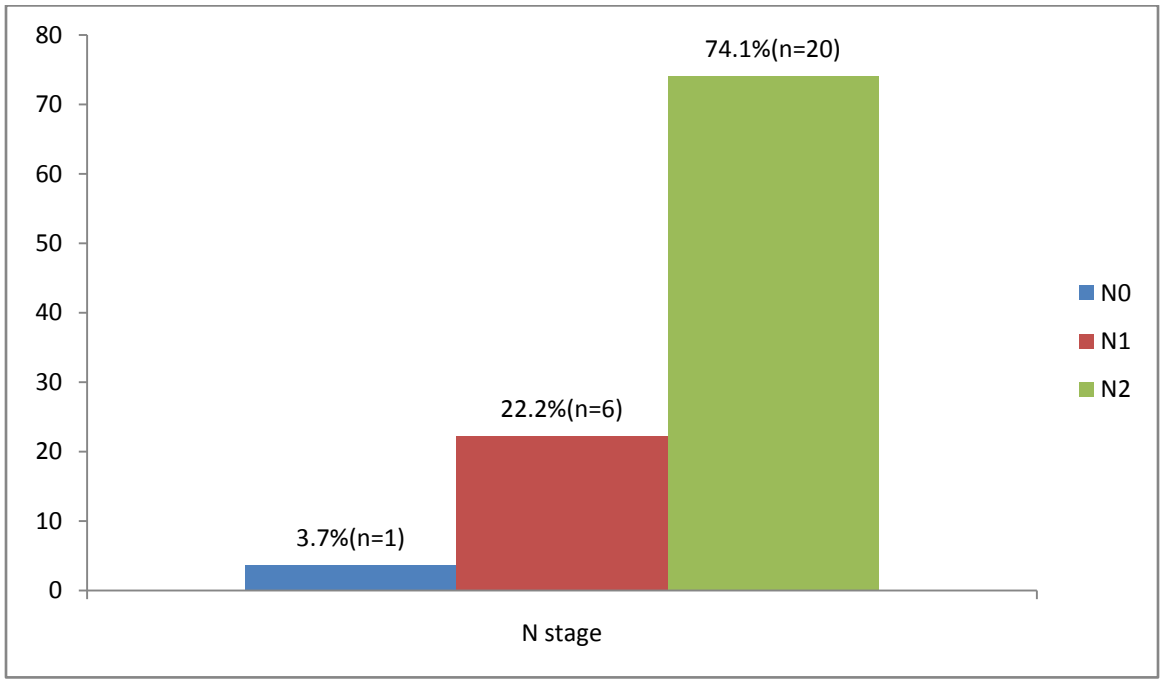


MRI axial section showing a mixed signal intensity tumor with infiltration of prostate- T4b disease

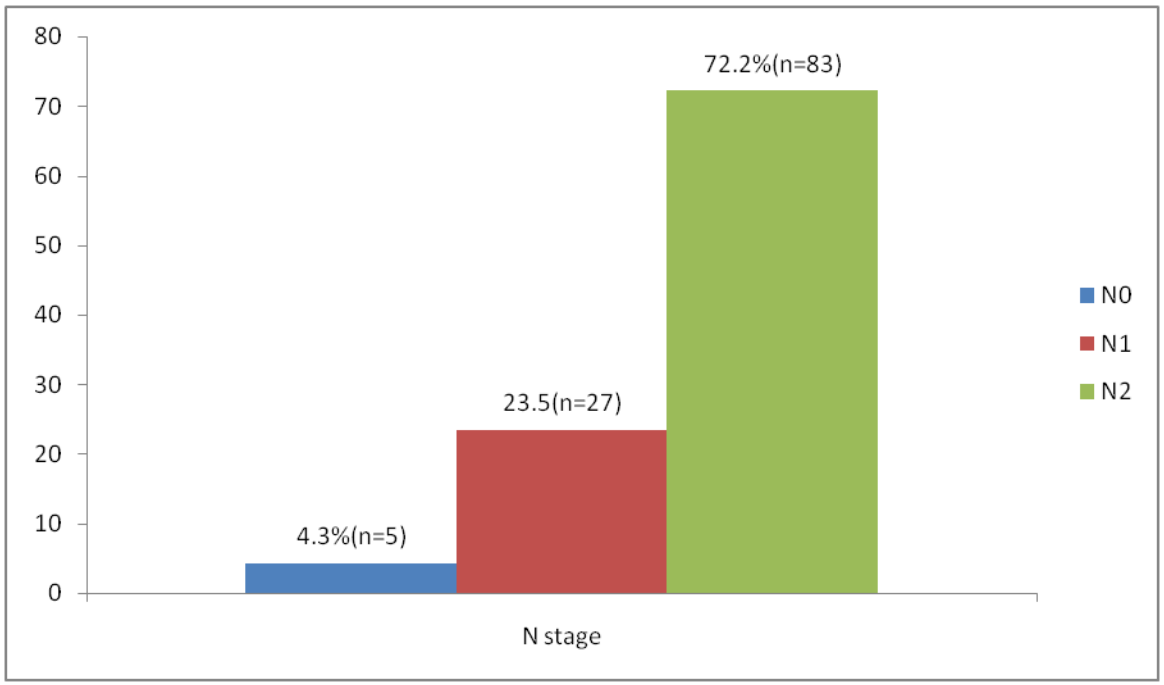
g) N stage of disease:

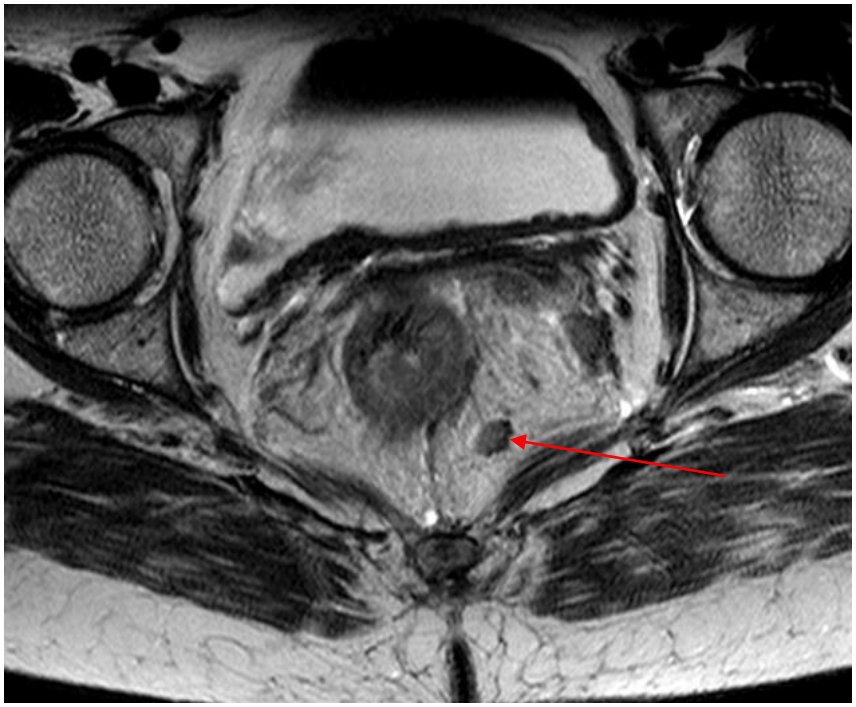
The incidence of N2 disease at presentation was higher in both age groups (74.1% in patients ≤25 years of age and 72.2% in patients>25 years of age)

i) In the younger age group (≤25 years of age):

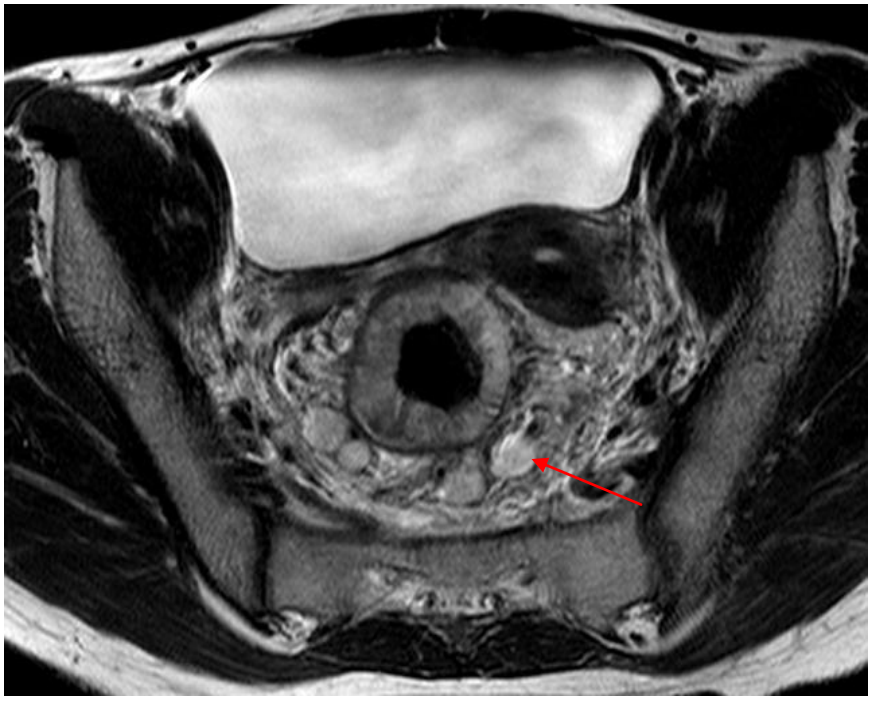


ii) In the older age group (>25 years of age):





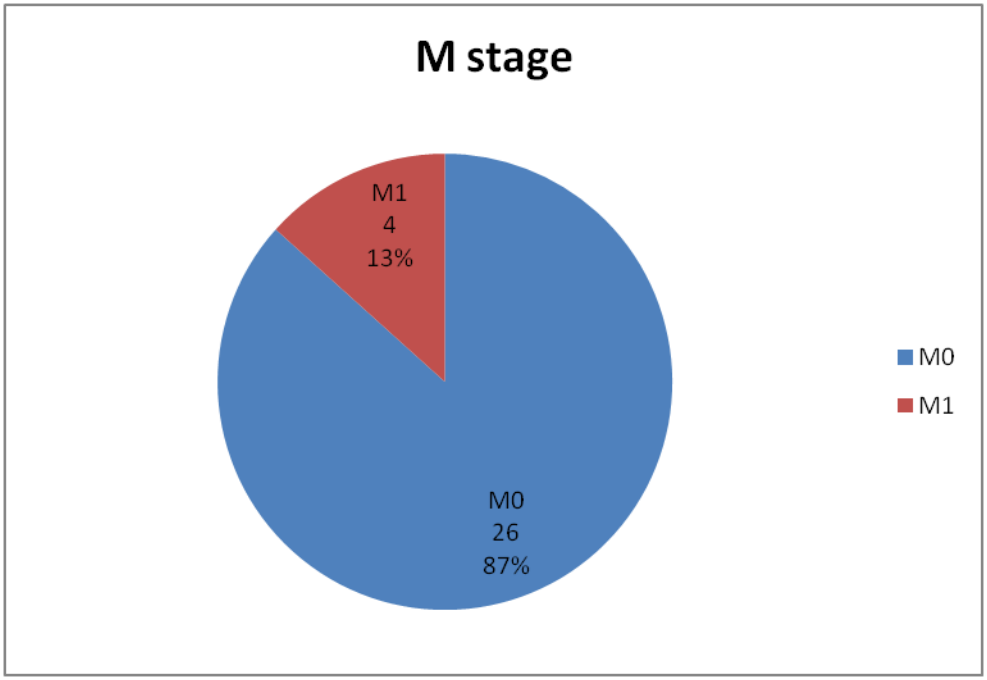
MRI axial section showing an intermediate signal rectal tumor and lymph nodes with irregular border, less than 3 in number - N1 disease



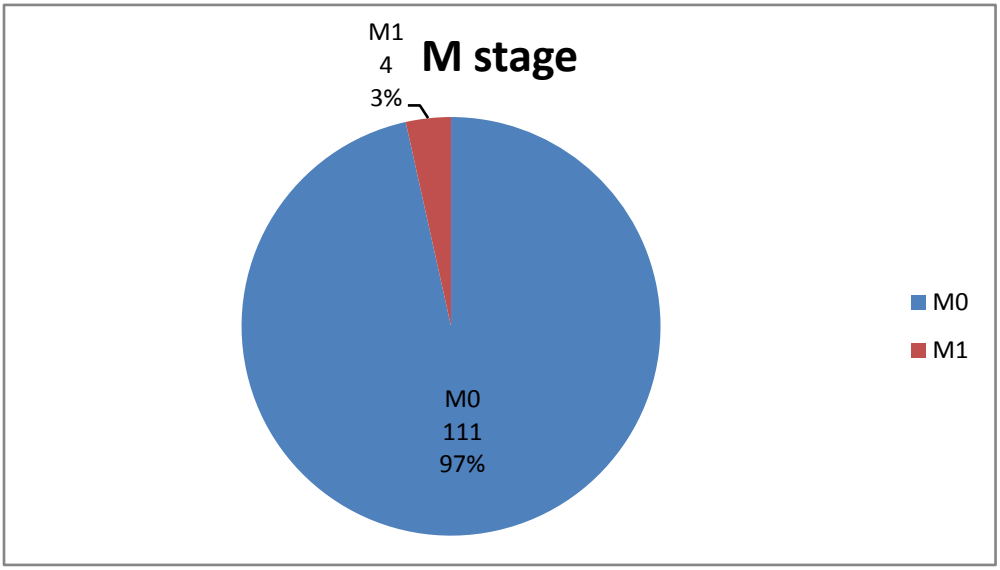
MRI axial section showing a high signal rectal tumor and multiple enlarged lymph nodes showing high signal intensity -more than 3 in number - N2 disease

h) M stage of disease

i) In the younger age group(≤25 years of age):



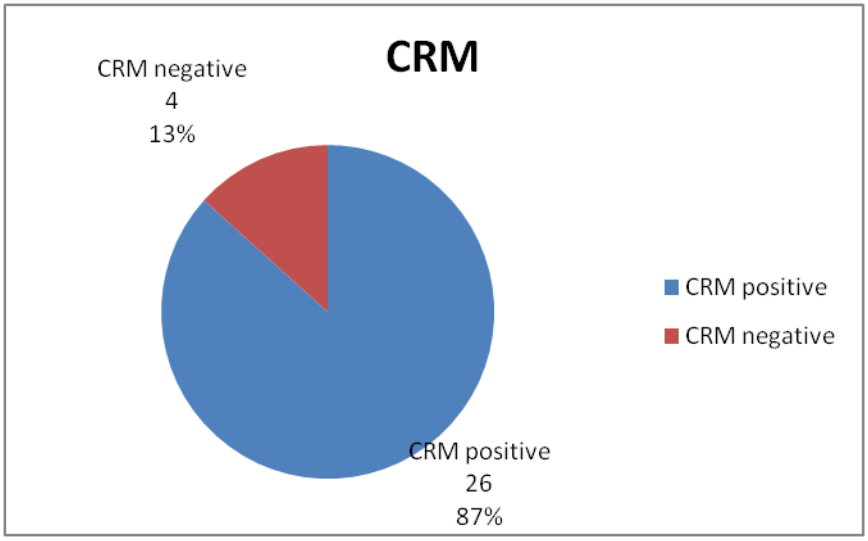
ii) In the older age group(>25 years of age):



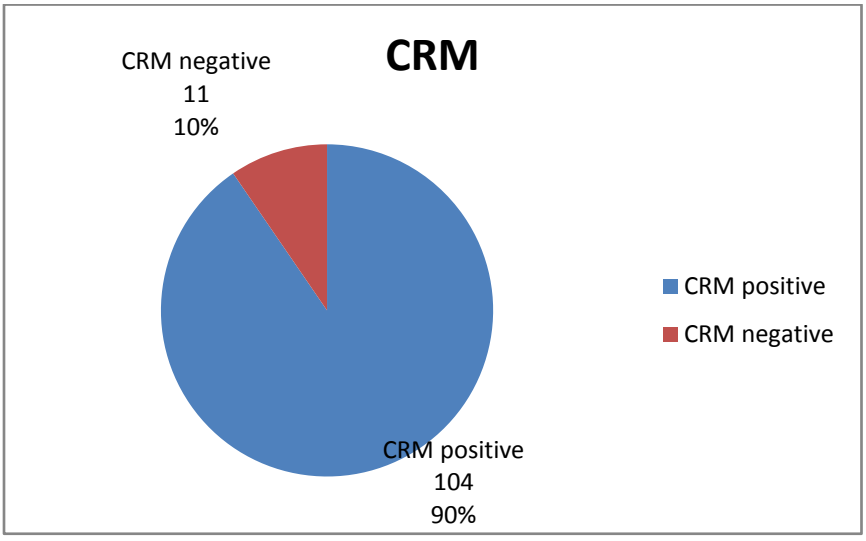
Most patients in both age groups had M0 disease.

i) Involvement of CRM

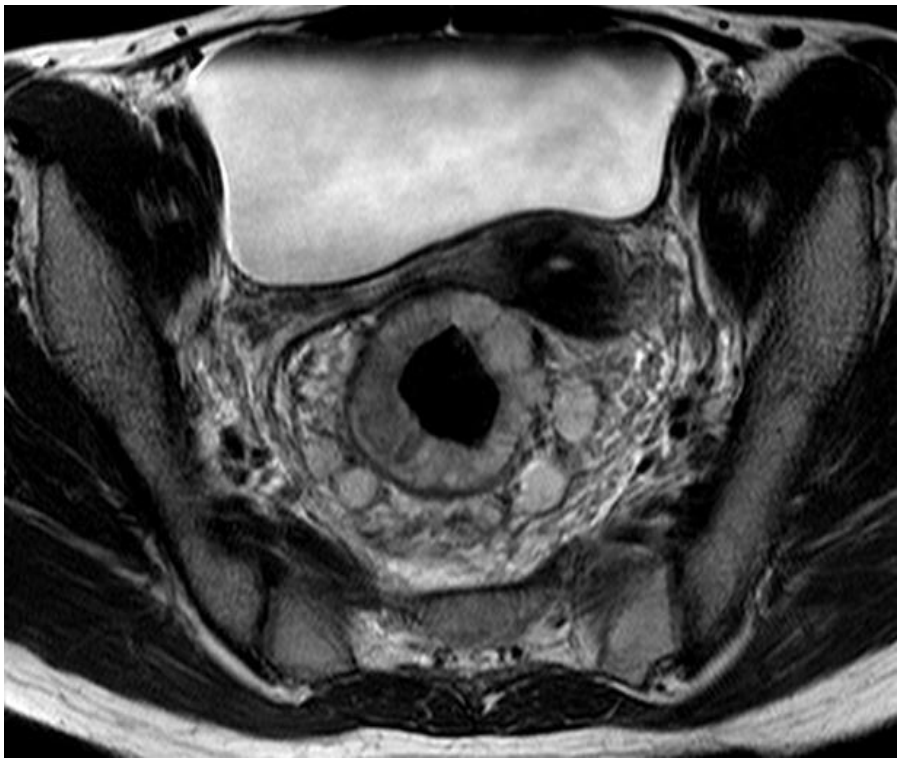
i) In the younger age group(≤25 years of age):



ii) In the older age group(>25 years of age):



Most patients in both age groups had involvement of CRM.

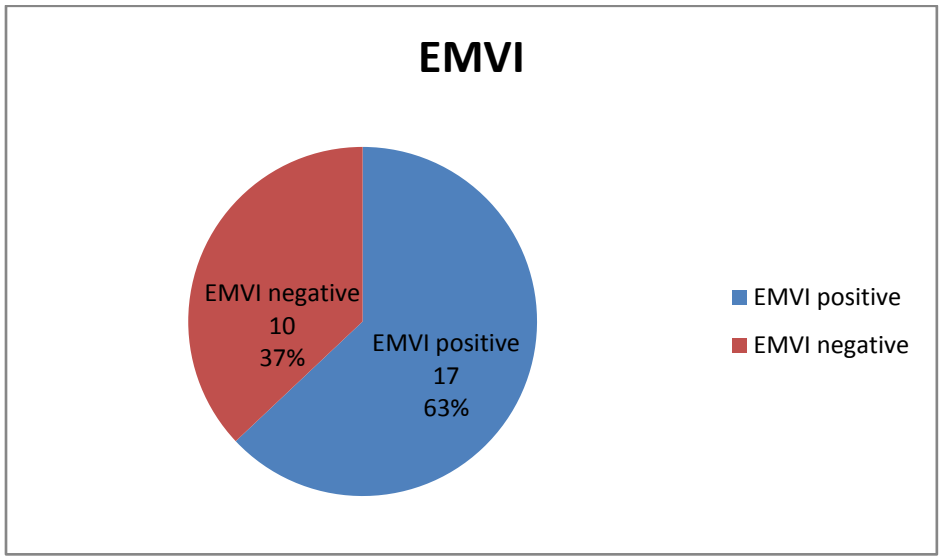


MRI axial section showing a high signal tumor with positive CRM

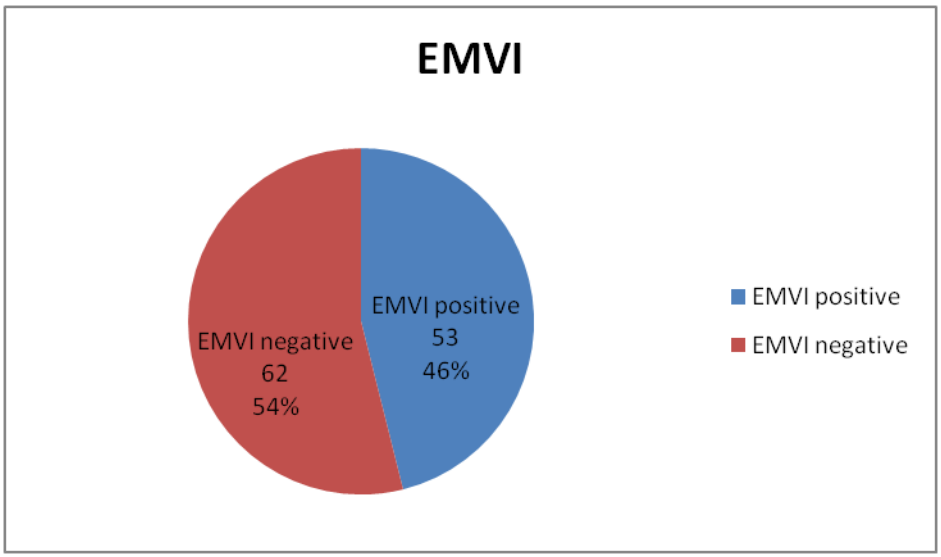
MRI axial section showing an intermediate signal tumor with negative CRM

j) Presence of extramural vascular invasion:

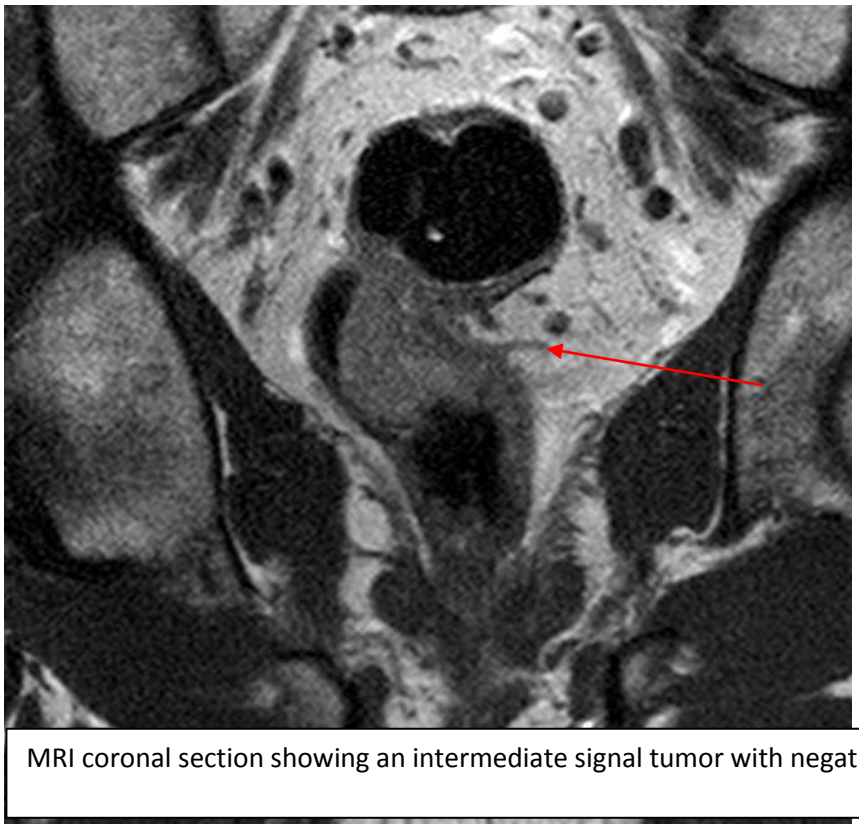
i) In the younger age group(≤25 years of age):



ii) In the older age group(>25 years of age):



The incidence of tumors with positive EMVI was higher (63%) in patients ≤25 years of age compared to patients >25 years of age (46%).



MRI coronal section showing an intermediate signal tumor with negative EMVI

MRI axial section showing an intermediate signal tumor with positive EMVI (vessel expanded with tumor signal intensity is seen at 6 O' clock position)

h) TNM stage in the initial staging MRI:

TNM stage	Stage 2	Stage 3	Stage 4
≤25 years of age	1 (3.7%)	25 (92.6%)	1 (3.7%)
>25 years of age	4 (3.5%)	107 (93%)	4 (3.5%)

Most patients in both age groups had stage 3 disease.

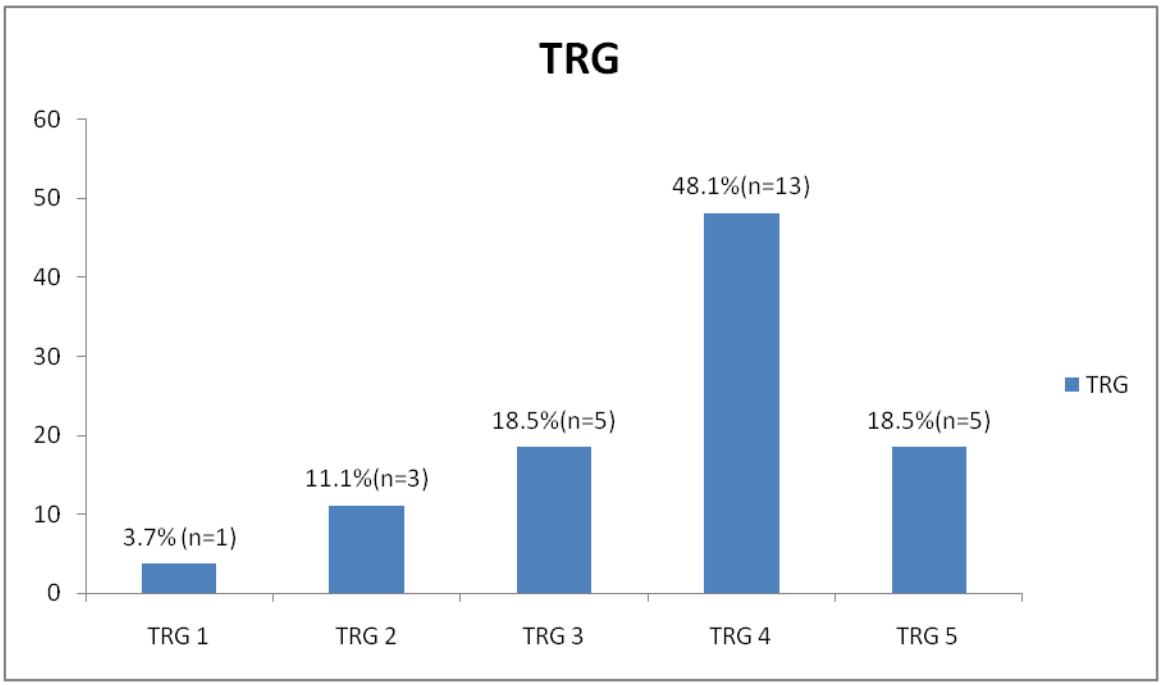
i) MRI tumor regression grading:

TRG 1, TRG 2 and TRG 3 were considered as good response group; whereas TRG 4 and TRG 5 were considered as poor response group.

- About 77 patients showed good response.

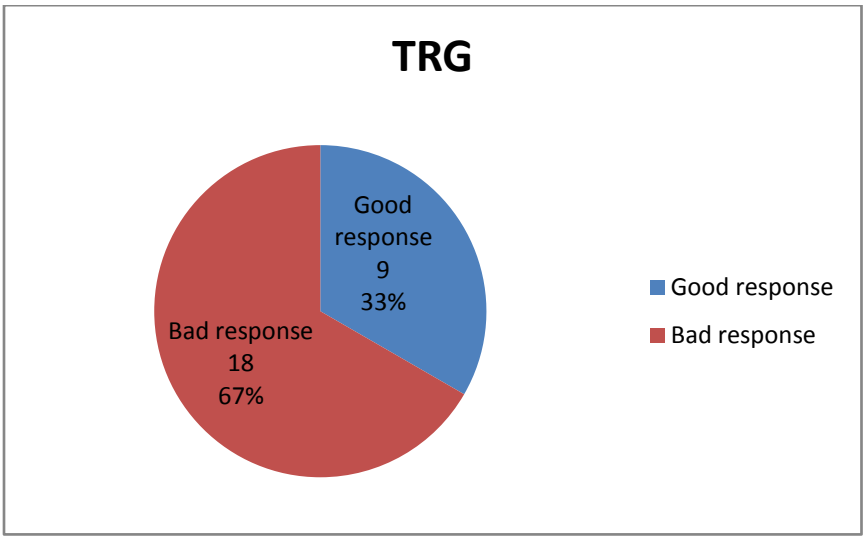
- About 65 patients showed poor response.

i)a) In the younger age group(≤25 years of age):

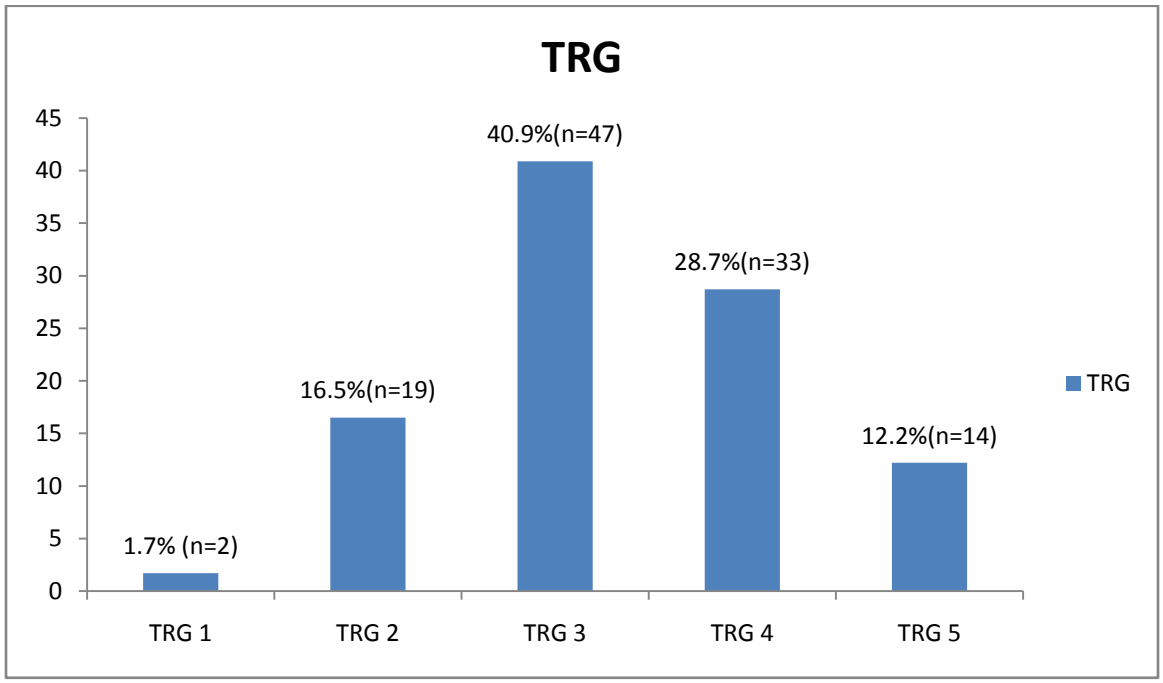


Majority of the tumors had tumor regression grade 4.

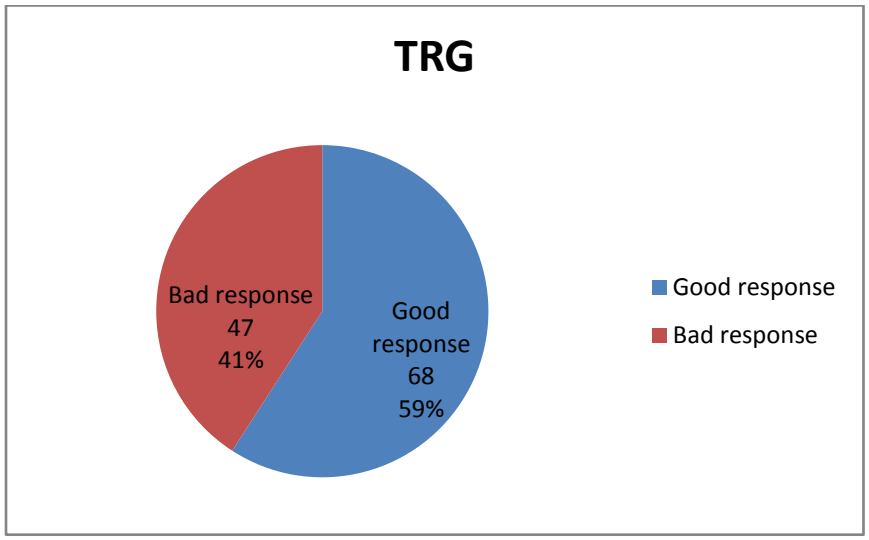
b) Comparison between good response (TRG1-3) and bad response(TRG4-5) in ≤25 years of age:

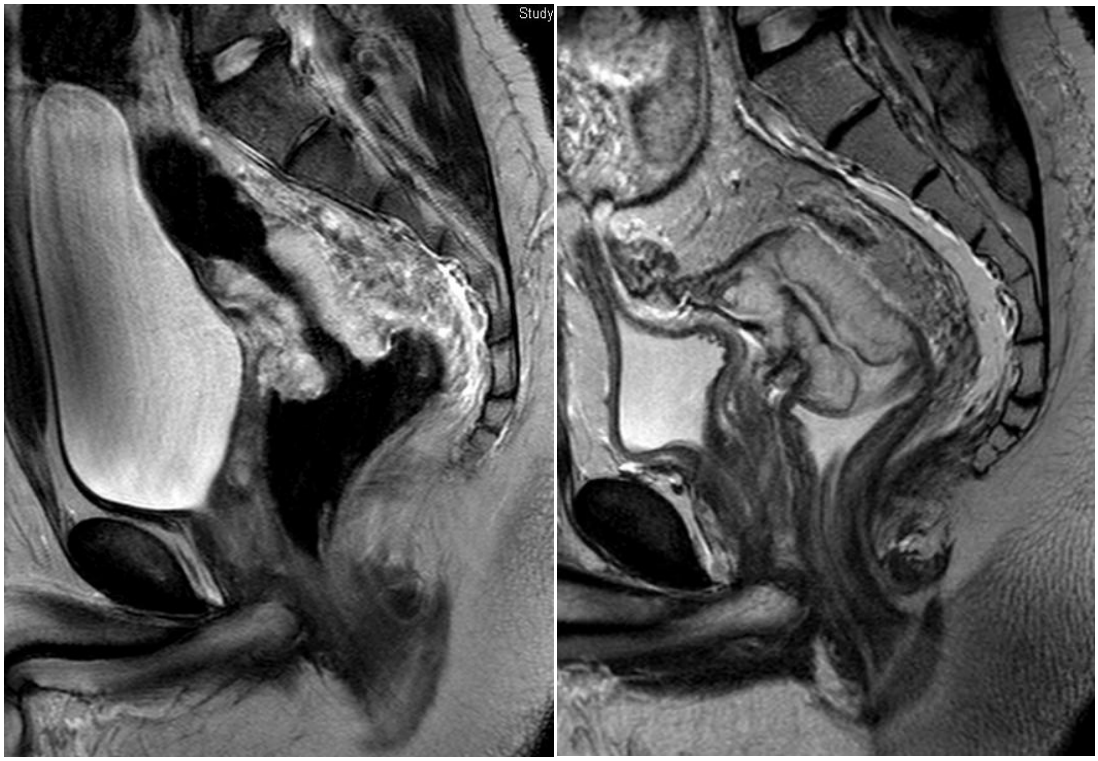


ii)a) In the older age group(>25 years of age):



b) Comparison between good response (TRG1-3) and bad response (TRG4-5) in >25 years of age:

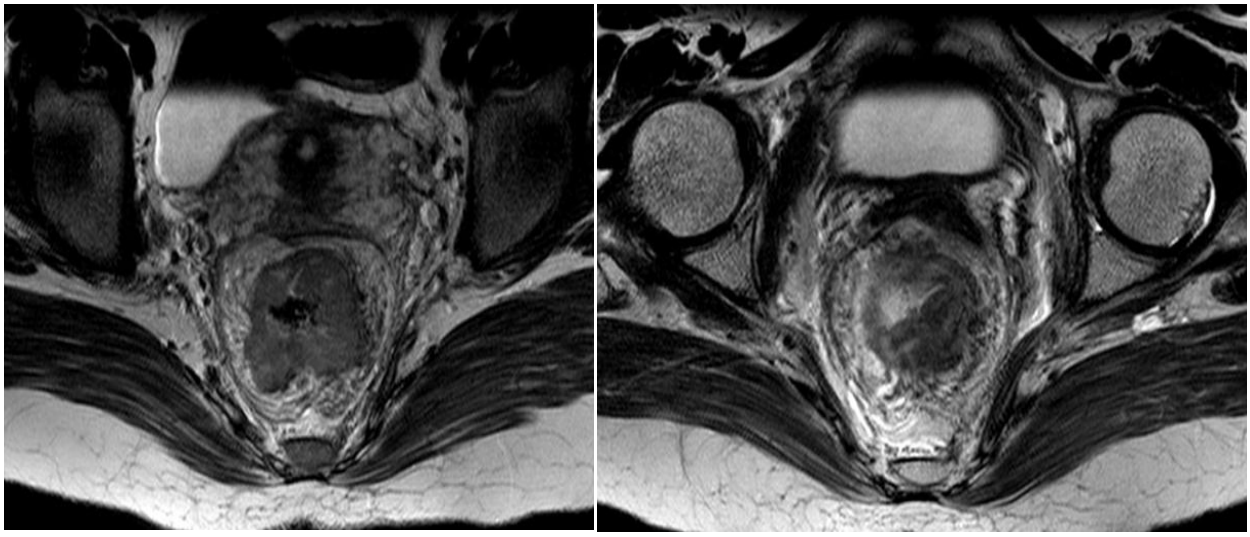




Pre- neoadjuvant therapy

Post- neoadjuvant therapy

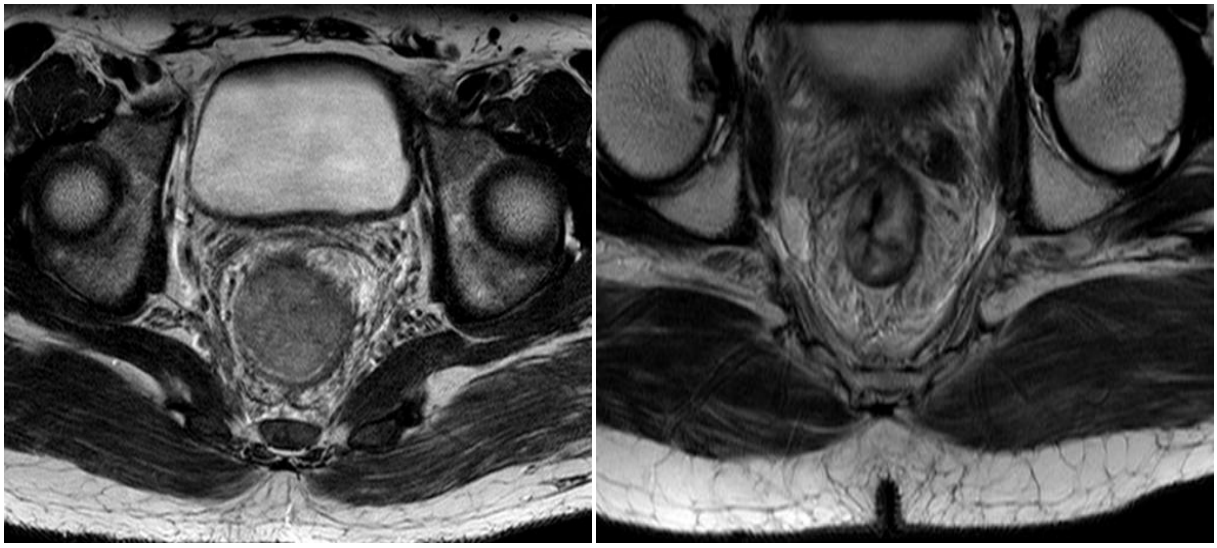
MRI axial sections of a patient with imaging before and after neoadjuvant therapy showing a high signal tumor which is unchanged from baseline –MRI TRG 5



Pre- neoadjuvant therapy

Post- neoadjuvant therapy

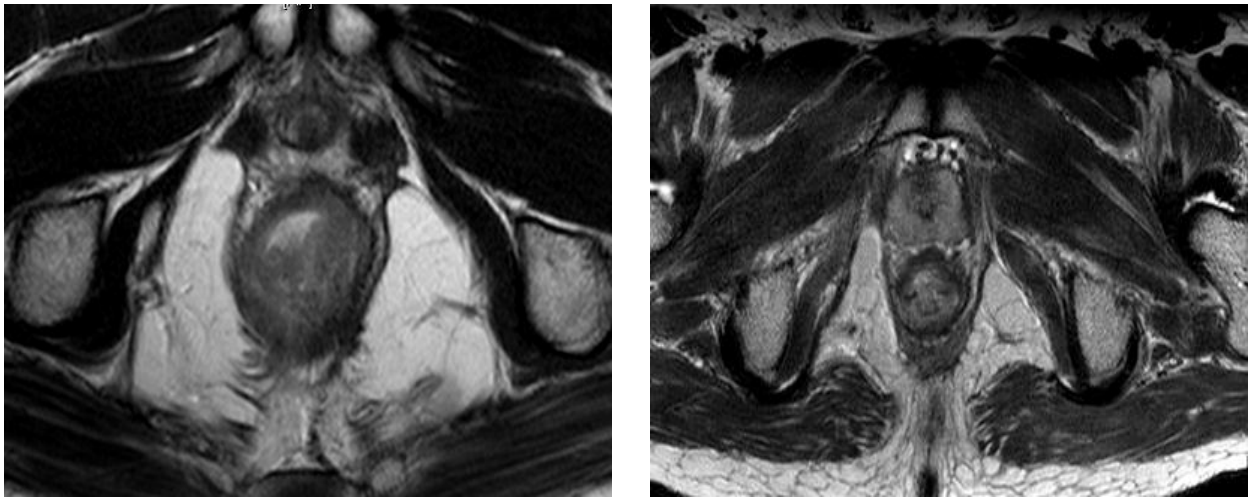
MRI axial sections of a patient with imaging before and after neoadjuvant therapy showing an intermediate signal tumor which shows predominant tumor signal intensity and mild mucinous change after neoadjuvant therapy –MRI TRG 4



Pre- neoadjuvant therapy

Post- neoadjuvant therapy

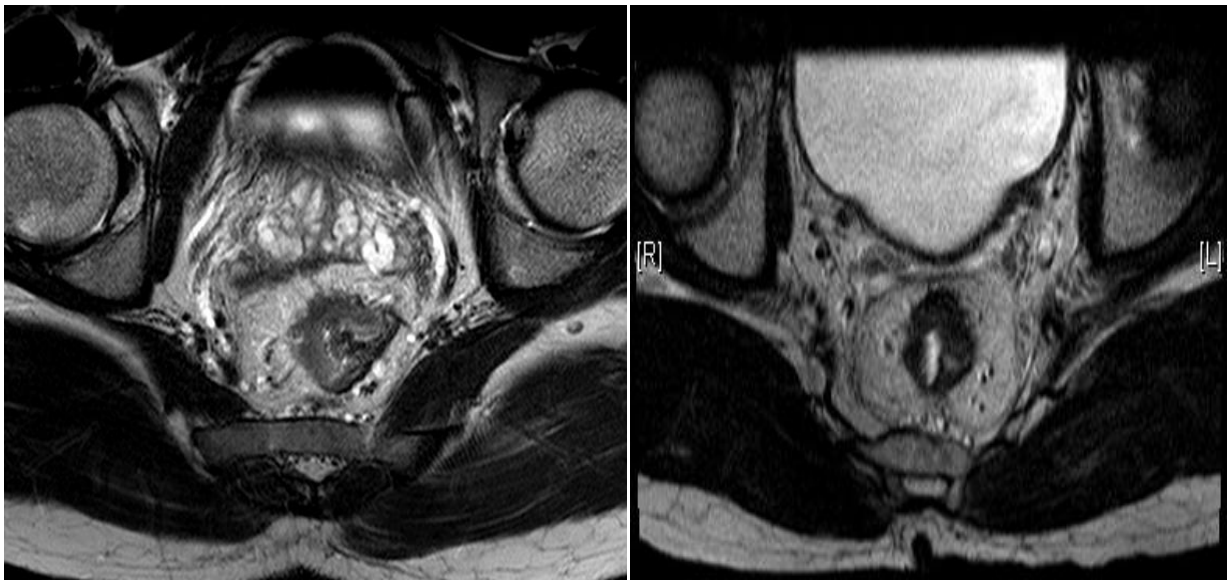
MRI axial sections of a patient with imaging before and after neoadjuvant therapy showing an intermediate signal tumor which shows more than 50% of mucinous change in post therapy imaging; however, tumor signal is still visible –MRI TRG 3



Pre- neoadjuvant therapy

Post- neoadjuvant therapy

MRI axial sections of a patient with imaging before and after neoadjuvant therapy showing an intermediate signal tumor which shows minimal residual tumor signal intensity and predominant fibrosis and mucinous change in post therapy imaging –MRI TRG 2



Pre- neoadjuvant therapy

Post- neoadjuvant therapy

MRI axial sections of a patient with imaging before and after neoadjuvant therapy showing an intermediate signal tumor which shows significant regression; no evident tumor signal in the post therapy imaging –MRI TRG 1

Bivariate analysis was performed to determine association between various factors:

I) Between younger (≤25 years of age) and older age (>25 years of age) groups:

-The following variables were analysed for association

a) Gender

b) Histological type of tumor (non-mucinous versus mucinous tumors)

- Both mucinous and signet ring cell cancers were grouped together as mucinous tumors

- Also, signet ring cell cancers were compared with other cancers.

c) Histological grade of tumor (poorly differentiated tumor which was considered as high grade versus well to moderately differentiated tumor which was grouped as low grade)

d) Location of the tumor (low rectal tumors versus upper and mid rectal tumors)

e) Signal intensity of the tumor on T2 weighted imaging (high signal versus intermediate to low signal)

f) T stage of the tumor (T1 and T2 were considered as early disease whereas T3 and T4 were considered as advanced T stage)

g) N stage

h) M stage (M0-absence of metastasis versus M1- presence of metastasis)

i) TNM stage (stage 1 and stage 2 were considered as early stage; whereas stage 3 and stage 4 were considered as advanced stage)

j) EMVI (presence and absence of EMVI)

k) TRG (TRG 1, TRG 2 and TRG 3 were considered as good response; whereas TRG 4 and TRG 5were considered as bad response.

Bivariate analysis of variables between the younger and older age groups:

Risk Variable	Age				p value
	≤25 years		>25 years		
	n	%	n	%	
Sex:					
Female	12	44.4	34	29.6	0.13
Male	15	55.6	81	70.4	
Histology:					
Non-mucinous	17	63.0	90	78.3	0.097
Mucinous	10	37.0	25	21.7	
Histology:					
Non signet ring cell cancers	20	74.1	98	85.2	0.16
Signet ring cell	7	25.9	17	14.8	
Histology grade:					
Well to moderate	16	64.0	76	73.8	0.32
Poorly differentiated	9	36.0	27	26.2	
Tumor location:					
Upper and mid rectal	13	48.1	40	34.8	0.196
Low rectal	14	51.9	75	65.2	
T2 signal intensity:					
High signal	13	48.1	22	19.3	0.002
Intermediate to low signal	14	51.9	92	80.7	
T stage:					
Early T stage	1	3.7	6	5.2	0.74
Advanced T stage	26	96.3	109	94.8	
N stage					
N0	1	3.7	5	4.3	0.98
N1	6	22.2	27	23.5	
N2	20	74.1	83	72.2	
M stage:					
Metastasis absent	26	96.3	111	96.5	1.00
Metastasis present	1	3.7	4	3.5	
TNM stage:					
Early stage	1	3.7	6	5.2	1.00
Advanced stage	26	96.3	109	94.8	
CRM:					
CRM positive	26	96.3	103	90.3	0.319
CRM negative	1	3.7	11	9.6	
EMVI:					
EMVI negative	10	37	62	53.9	0.114
EMVI positive	17	63	53	46.1	
TRG:					
Good response	9	33.3	68	59.1	0.01
Bad response	18	66.7	47	40.9	

Interpretation:

i) The incidence of T2 high signal intensity in younger (≤25 years of age) age group was 48.1% compared to 19.3% in the older age group and this was statistically significant (p value of <0.05).

ii) The restaging MRI in young patients showed poorer MRI tumor regression grade (66.7%) compared to older patients (40.9%) which was statistically significant (p value of 0.01)

iii) The incidence of mucinous cancers among younger patients who underwent neoadjuvant therapy was 37% compared to 21.7% in the older age group. However, the difference among older and younger age groups was not statistically significant.

iv) The incidence of signet ring cell cancers among younger patients who underwent neoadjuvant therapy is 25.9% compared to 14.8% in the older age group. The difference in the incidence among younger and older groups was not statistically significant.

v) The incidence of high grade (poorly differentiated) tumors was 36% in the younger age group compared to 26.2% in older patients (p value = 0.32)

II) a) Comparison between the good response and poor response groups:

Among the good response group:

i) Age:

- 68 patients (88.3%) were above 25 years of age and 9 patients (33.3%) were below 25 years of age.

ii) Gender:

- 55 patients (71.4%) were women.

- 22 patients (28.6%) were men.

iii) Histology of tumor:

- 69 patients (89.6%) with non-mucinous tumors

- 8 patients (10.4%) with mucinous tumors

iv) Histological grade:

- 59 patients (85.5%) with well to moderately differentiated cancers

-10 patients (14.5%) with poorly differentiated tumors

v) Tumor location:

- 30 patients (39%) with mid and upper rectal tumors

- 47 patients (61%) with low rectal tumors

vi) T2 signal intensity:

- 6 patients (7.9%) with high T2 signal tumors

- 70 patients (92.1%) with mixed signal tumors

b) Bivariate analysis was also done to determine association between factors causing good response and bad response.

The various factors seen in both good response group and poor response groups were compared:

a) Age: below 25 years and above 25 years

b) Gender

c) Histology of the tumor – mucinous versus non-mucinous

d) Histological grade of the tumor (high grade versus low grade)

e) Tumor location (low rectal versus mid and upper rectal)

f) T2 signal intensity of the tumor (high signal versus intermediate to low signal)

g) T stage of the tumor (T2 – early disease versus T3 and T4-advanced disease)

h) Presence of CRM

i) Presence of EMVI

Bivariate analysis (between good response and bad response groups):

Risk Variable	MRI TRG				p value
	Good response		Bad response		
	n	%	n	%	
Age					
≤25 years	9	33.3	18	66.7	0.015
>25 years	68	59.1	47	40.9	
Sex:					
Female	22	47.8	24	52.2	0.28
Male	55	57.3	41	42.7	
Histology:					
Non-mucinous	69	64.5	38	35.5	0.00
Mucinous	8	22.9	27	77.1	
Histology:					
Non-signet cell	73	61.9	45	38.1	0.00
Signet cell	4	16.7	20	83.3	
Histology grade:					
Well to moderate	59	64.1	33	35.9	0.00
Poorly differentiated	10	27.8	26	44.1	
Tumor location:					
Upper and mid rectal	30	56.6	23	43.4	0.66
Low rectal	47	52.8	42	47.2	
T2 signal intensity:					
High signal	6	17.1	29	82.9	0.00
Intermediate to low signal	70	66	36	34	
T stage:					
Early T stage	5	71.4	2	28.6	0.35
Advanced T stage	72	53.3	163	46.7	
N stage:					
N0	3	50	3	50	0.26
N1	22	66.7	11	33.3	
N2	52	50.5	51	49.5	
M stage:					
M0	76	55.5	61	44.5	0.12
M1	1	20	4	80	
CRM:					
CRM positive	68	52.7	61	47.3	0.13
CRM negative	9	75	3	25	
EMVI:					
EMVI negative	49	68.1	23	31.9	0.001
EMVI positive	28	40	42	60	

Interpretation:

i) 66.7% of patients younger than 25 years of age showed poor tumor regression grade.

ii) 77.1% of mucinous tumors showed poor tumor regression grade

iii) 64.6% of EMVI positive tumors showed poor tumor regression grade.

iv) 82.9% of high signal tumors showed poor tumor regression grade.

v) 72.2% of high grade tumors showed poor response.

vi) Also, 83.3% of signet cell tumors showed poor response.

III) Multivariate regression analysis was done to determine the factors predicting bad response as outcome.

- The following factors were assessed

i) Age

ii) Gender

iii) Tumor histology (mucinous versus non-mucinous)

iv) Tumor grade (poorly differentiated verus well to moderately differentiated)

v) Tumor location (low rectal versus upper and mid rectal)

vi) T2 signal intensity of tumor (high signal versus intermediate to low signal)

vii) T stage of tumor (T2-early versus advanced-T3 and T4 disease)

viii) Involvement of CRM (positive versus negative)

ix) Presence of EMVI (presence of EMVI versus absence of EMVI)

Multivariate regression analysis to predict poor response on MRI:

Risk Variable	OR	95% CI	p value
Age: ≤25 >25	 2.05 1.00	0.61 – 6.89	0.24
Gender: Female Male	 2.50 1.00	0.43-6.66	0.07
Tumor histology: Mucinous Non-mucinous	 5.53 1.00	0.92-33.2	0.06
Tumor grade: Poorly differentiated Well to moderately differentiated	 1.38 1.00	0.38-5.02	0.62
Tumor location: Upper rectal Low rectal	 0.97 1.00	0.38-2.51	0.96
Tumor T2 signal intensity: High signal Intermediate to low signal	 6.28 1.00	1.48-26.55	0.01
T stage of tumor: Advanced stage Early stage	 0.46 1.00	0.06-3.12	0.43
CRM involvement: CRM positive CRM negative	 1.31 1.00	0.23-7.26	0.76
EMVI involvement: EMVI positive EMVI negative	 4.17 1.00	1.55-11.19	0.005

IV) Comparison between mucinous and non-mucinous tumors:

T2 signal intensity	Histology				p value
	Non-mucinous		Mucinous		
	n	%	n	%	
High signal	10	28.6	25	71.4	0.00
Intermediate to low signal	96	90.6	10	9.4	

71.4% of rectal tumors with high T2 signal intensity were mucinous tumors; which is statistically significant (p=0.00).

V) Sensitivity and specificity of T2 high signal in predicting mucinous tumors:

		Histology: Mucinous	Histology: Non-mucinous
MRI	T2 high signal	25	10
	T2 intermediate to low signal	10	96

Sensitivity - 71.4%

Specificity- 90.6%

Positive predictive value – 71.4%

Negative predictive value – 90.6%

DISCUSSION:

a) Patient demographics:

Gender

i) There was no significant difference in gender distribution among younger and older age groups.

b) Tumor characteristics on histology:

i) Among young patients who underwent neoadjuvant therapy, the incidence of mucinous tumors was high (37%) compared to 21.7% in older age group. Among these tumors, most of the tumors were signet ring cell cancers- 25.9% compared to 14.8% in older age group.However, this was not statistically significant.

ii) The incidence of poorly differentiated tumors in patients ≤25 years of age is more, 36% compared to 26.2% in patients >25 years of age. This difference did not show statistical significance.

c) Tumor characteristics on MRI:

i) Tumor location

Most of the young patients who underwent neoadjuvant therapy had low rectal tumors (incidence of 51.9%). A similar pattern was seen in the older patients with an incidence of 65.2%)

ii) Type of tumor

Most of the patients in both age groups had circumferential tumors- 66.7% in patients ≤25 years of age and 65.2% in patients>25 years of age.

iii) T2 signal intensity of tumor:

The incidence of high T2 signal tumors in patients ≤25 years of age was higher (48.1%) compared to patients >25 years of age (19.3%). The difference in the incidence of T2 high signal tumors among these age groups was statistically significant.

iv) Circumferential resection margin:

The incidence of tumors in which involvement of CRM was present was similarly high in patients≤25 years of age (96.3%) and patients>25 years of age (96.5%). This is probably because involvement of CRM in locally advanced rectal tumors is one of the indication for neoadjuvant treatment.

v) EMVI:

The incidence of tumors with positive EMVI was higher (63%) in patients ≤25 years of age compared to 46.1% in patients>25 years of age.

vi) T stage and N stage:

Most patients in both groups had T3 stage and N2 disease (74.1% in patients ≤25 years of age and 72.2% in patients >25 years of age).

vii) TNM stage:

Patients in both age groups, that is, ≤25 years of age and >25 years of age, presented more with stage 3 disease.

viii) MRI tumor regression grade:

Poorer tumor regression grade (4 and 5) were seen more in patients ≤25 years of age (incidence of 66.7% compared to 40.9% in patients >25 years of age).

B) Bivariate analysis was done to assess the factors with significant association with tumor regression grade.

a) The following parameters were identified to have significant association with poor response (TRG 4 and 5):

i) Age ≤25 years of age

ii) Mucinous tumors

ii) Poorly differentiated tumors

iii) Tumors with T2 high signal

iv) Tumors with positive extramural vascular invasion

b) Other factors like gender, tumor location and involvement of CRM did not affect outcome.

C) Multivariate analysis was also done to assess the independent factors causing poor response to therapy

- The following factors were identified as independent factors causing poor tumor regression grade.

i) T2 high signal intensity of the tumor

ii) Presence of EMVI

iii) Mucinous tumor (borderline statistically significant; p value of 0.06)

iv) Female gender (borderline statistically significant; p value of 0.07)

D) The sensitivity and specificity of T2 high signal intensity for predicting mucinous tumor are 71.4% and 90.6% respectively.

CONCLUSIONS:

i) Patients ≤25 years of age had poorer tumor regression grades (TRG 4 and TRG 5) following neoadjuvant therapy compared to those >25 years of age.

ii) Patients ≤25 years of age had a higher incidence of tumors with high T2 signal intensity compared to those >25 years of age.

iii) The factors significantly associated with poor tumor regression grades were

- age ≤ 25 years
- mucinous tumors
- poorly differentiated tumors
- High T2 signal intensity of the tumor on MRI
- Presence of EMVI

iv) High T2 signal intensity of tumor and presence of EMVI were two independent predictors of poor response to neoadjuvant therapy.

LIMITATIONS:

i) The study only included only those patients who had MRI as initial imaging. Those patients who had CT as initial imaging or for restaging were excluded.Since young patients are more likely to present with advanced disease, they might have had a CT as initial imaging and might not have had an MRI examination.

ii) There was no histopathological correlation of tumor regression grade; as many patients did not undergo surgery due to poor response to neoadjuvant therapy.

REFERENCES:

1. Haggar FA, Boushey RP. Colorectal Cancer Epidemiology: Incidence, Mortality, Survival, and Risk Factors. Clin Colon Rectal Surg. 2009 Nov;22(4):191–7.

2. Dozois EJ, Boardman LA, Suwanthanma W, Limburg PJ, Cima RR, Bakken JL, et al. Young-onset colorectal cancer in patients with no known genetic predisposition: can we increase early recognition and improve outcome? Medicine (Baltimore). 2008 Sep;87(5):259–63.

3. Ahnen DJ, Wade SW, Jones WF, Sifri R, Mendoza Silveiras J, Greenamyer J, et al. The increasing incidence of young-onset colorectal cancer: a call to action. Mayo Clin Proc. 2014 Feb;89(2):216–24.

4. Fu J, Yang J, Tan Y, Jiang M, Wen F, Huang Y, et al. Young Patients (≤35years old) With Colorectal Cancer Have Worse Outcomes Due to More Advanced Disease: A 30-Year Retrospective Review. Medicine (Baltimore). 2014 Nov;93(23):e135.

5. Mekenkamp LJM, Heesterbeek KJ, Koopman M, Tol J, Teerenstra S, Venderbosch S, et al. Mucinous adenocarcinomas: poor prognosis in metastatic colorectal cancer. Eur J Cancer Oxf Engl 1990. 2012 Mar;48(4):501–9.

6. Kaur H, Choi H, You YN, Rauch GM, Jensen CT, Hou P, et al. MR imaging for preoperative evaluation of primary rectal cancer: practical considerations. Radiogr Rev Publ Radiol Soc N Am Inc. 2012 Apr;32(2):389–409.

7. Halappa VG, Villalobos CPC, Bonekamp S, Gearhart SL, Efron J, Herman J, et al. Rectal Imaging: Part I, High-Resolution MRI of Carcinoma of the Rectum at 3 T. AJR Am J Roentgenol. 2012 Jul;199(1):W35–42.

8. Patel UB, Blomqvist LK, Taylor F, George C, Guthrie A, Bees N, et al. MRI after treatment of locally advanced rectal cancer: how to report tumor response--the MERCURY experience. AJR Am J Roentgenol. 2012 Oct;199(4):W486–95.

9. Patel UB, Taylor F, Blomqvist L, George C, Evans H, Tekkis P, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol Off J Am Soc Clin Oncol. 2011 Oct 1;29(28):3753–60.

10. Nath J, Wigley C, Keighley MRB, Perakath B. Rectal cancer in young adults: a series of 102 patients at a tertiary care centre in India. Colorectal Dis Off J Assoc Coloproctology G B Irel. 2009 Jun;11(5):475–9.

11. Boyle P, Langman JS. ABC of colorectal cancer: Epidemiology. BMJ. 2000 Sep 30;321(7264):805–8.

12. Mohandas KM. Colorectal cancer in India: controversies, enigmas and primary prevention. Indian J Gastroenterol Off J Indian Soc Gastroenterol. 2011 Feb;30(1):3–6.

13. Javid G, Zargar SA, Rather S, Khan AR, Khan BA, Yattoo GN, et al. Incidence of colorectal cancer in Kashmir valley, India. Indian J Gastroenterol Off J Indian Soc Gastroenterol. 2011 Feb;30(1):7–11.

14. Peedikayil MC, Nair P, Seena SM, Radhakrishnan L, Sadasivan S, Naryanan VA, et al. Colorectal cancer distribution in 220 Indian patients undergoing colonoscopy. Indian J Gastroenterol Off J Indian Soc Gastroenterol. 2009 Dec;28(6):212–5.

15. Pathy S, Lambert R, Sauvaget C, Sankaranarayanan R. The incidence and survival rates of colorectal cancer in India remain low compared with rising rates in East Asia. Dis Colon Rectum. 2012 Aug;55(8):900–6.

16. Chen LK, Hwang SJ, Li AF, Lin JK, Wu TC. Colorectal cancer in patients 20 years old or less in Taiwan. South Med J. 2001 Dec;94(12):1202–5.

18. Chan K, Dassanayake B, Deen R, Wickramarachchi R, Kumarage S, Samita S, et al. Young patients with colorectal cancer have poor survival in the first twenty months after operation and predictable survival in the medium and long-term: Analysis of survival and prognostic markers. World J Surg Oncol. 2010 Sep 15;8:82.

19. Leff DR, Chen A, Roberts D, Grant K, Western C, Windsor ACJ, et al. Colorectal cancer in the young patient. Am Surg. 2007 Jan;73(1):42–7.

20. Iafrate F, Laghi A, Paolantonio P, Rengo M, Mercantini P, Ferri M, et al. Preoperative Staging of Rectal Cancer with MR Imaging: Correlation with Surgical and Histopathologic Findings. RadioGraphics. 2006 May 1;26(3):701–14.

21. Arya S, Das D, Engineer R, Saklani A. Imaging in rectal cancer with emphasis on local staging with MRI. Indian J Radiol Imaging. 2015;25(2):148–61.

22. Boyle P, Leon ME. Epidemiology of colorectal cancer. Br Med Bull. 2002 Dec 1;64(1):1–25.

23. Amersi F, Agustin M, Ko CY. Colorectal Cancer: Epidemiology, Risk Factors, and Health Services. Clin Colon Rectal Surg. 2005 Aug;18(3):133–40.

24. Sandler RS. Epidemiology and risk factors for colorectal cancer. Gastroenterol Clin North Am. 1996 Dec;25(4):717–35.

25. MERCURY Study Group. Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. Radiology. 2007 Apr;243(1):132–9.

26. Fleming M, Ravula S, Tatishchev SF, Wang HL. Colorectal carcinoma: Pathologic aspects. J Gastrointest Oncol. 2012 Sep;3(3):153–73.

27. Leopoldo S, Lorena B, Cinzia A, Gabriella DC, Angela Luciana B, Renato C, et al. Two subtypes of mucinous adenocarcinoma of the colorectum: clinicopathological and genetic features. Ann Surg Oncol. 2008 May;15(5):1429–39.

28. Kang H, O'Connell JB, Maggard MA, Sack J, Ko CY. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum. 2005 Jun;48(6):1161–8.

29. Yu SKT, Chand M, Tait DM, Brown G. Magnetic resonance imaging defined mucinous rectal carcinoma is an independent imaging biomarker for poor prognosis and poor response to preoperative chemoradiotherapy. Eur J Cancer Oxf Engl 1990. 2014 Mar;50(5):920–7.

30. Chen J-S, Hsieh P-S, Chiang J-M, Yeh C-Y, Tsai W-S, Tang R, et al. Clinical outcome of signet ring cell carcinoma and mucinous adenocarcinoma of the colon. Chang Gung Med J. 2010 Feb;33(1):51–7.

31. Trakarnsanga A, Gonen M, Shia J, Goodman KA, Nash GM, Temple LK, et al. What is the significance of the circumferential margin in locally advanced rectal cancer after neoadjuvant chemoradiotherapy? Ann Surg Oncol. 2013 Apr;20(4):1179–84.

32. Schrag D. Evolving role of neoadjuvant therapy in rectal cancer. Curr Treat Options Oncol. 2013 Sep;14(3):350–64.

33. Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol Off J Eur Soc Med Oncol ESMO. 2012 Oct;23(10):2479–516.

34. Keum MA, Lim S-B, Kim SA, Yoon YS, Kim CW, Yu CS, et al. Clinicopathologic Factors Affecting Recurrence after Curative Surgery for Stage I Colorectal Cancer. J Korean Soc Coloproctology. 2012 Feb;28(1):49–55.

35. Schrag D. Evolving role of neoadjuvant therapy in rectal cancer. Curr Treat Options Oncol. 2013 Sep;14(3):350–64.

36. Bujko K, Bujko M. Point: short-course radiation therapy is preferable in the neoadjuvant treatment of rectal cancer. Semin Radiat Oncol. 2011 Jul;21(3):220–7.

37. Stewart DB, Dietz DW. Total Mesorectal Excision: What Are We Doing? Clin Colon Rectal Surg. 2007 Aug;20(3):190–202.

38. Arbman G, Nilsson E, Hallböök O, Sjödahl R. Local recurrence following total mesorectal excision for rectal cancer. Br J Surg. 1996 Mar;83(3):375–9.

39. Cecil TD, Sexton R, Moran BJ, Heald RJ. Total mesorectal excision results in low local recurrence rates in lymph node-positive rectal cancer. Dis Colon Rectum. 2004 Jul;47(7):1145–9; discussion 1149–50.

40. Bergamaschi R, Pessaux P, Burtin P, Arnaud JP. Abdominoperineal resection for locally recurrent rectal cancer. Tech Coloproctology. 2001 Aug;5(2):97–102.

41. Cai Y, Li Z, Gu X, Fang Y, Xiang J, Chen Z. Prognostic factors associated with locally recurrent rectal cancer following primary surgery (Review). Oncol Lett. 2014 Jan;7(1):10–6.

42. Zampino MG, Magni E, Leonardi MC, Petazzi E, Santoro L, Luca F, et al. Capecitabine initially concomitant to radiotherapy then perioperatively administered in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. 2009 Oct 1;75(2):421–7.

43. Gao Y-H, Zhang X, An X, Cai M-Y, Zeng Z-F, Chen G, et al. Oxaliplatin and capecitabine concomitant with neoadjuvant radiotherapy and extended to the resting period in high risk locally advanced rectal cancer. Strahlenther Onkol Organ Dtsch Röntgenges Al. 2014 Feb;190(2):158–64.

44. van Dijk TH, Tamas K, Beukema JC, Beets GL, Gelderblom AJ, de Jong KP, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. Ann Oncol Off J Eur Soc Med Oncol ESMO. 2013 Jul;24(7):1762–9.

45. Garcia-Aguilar J, Smith DD, Avila K, Bergsland EK, Chu P, Krieg RM, et al. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg. 2011 Jul;254(1):97–102.

46. Boland PM, Fakih M. The emerging role of neoadjuvant chemotherapy for rectal cancer. J Gastrointest Oncol. 2014 Oct;5(5):362–73.

47. Compton CC. Pathologic prognostic factors in the recurrence of rectal cancer. Clin Colorectal Cancer. 2002 Nov;2(3):149–60.

48. Halappa VG, Villalobos CPC, Bonekamp S, Gearhart SL, Efron J, Herman J, et al. Rectal Imaging: Part I, High-Resolution MRI of Carcinoma of the Rectum at 3 T. AJR Am J Roentgenol. 2012 Jul;199(1):W35–42.

49. Brown G, Radcliffe AG, Newcombe RG, Dallimore NS, Bourne MW, Williams GT. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. Br J Surg. 2003 Mar;90(3):355–64.

50. Iafrate F, Laghi A, Paolantonio P, Rengo M, Mercantini P, Ferri M, et al. Preoperative staging of rectal cancer with MR imaging: correlation with surgical and histopathologic findings1. Radiographics. 2006;26(3):701–14.

51. Nougaret S, Reinhold C, Mikhael HW, Rouanet P, Bibeau F, Brown G. The use of MR imaging in treatment planning for patients with rectal carcinoma: have you checked the "DISTANCE"? Radiology. 2013 Aug;268(2):330–44.

52. Microsoft Word - FINAL_USER'S GUIDE April 23 2012.doc - UserFile.aspx [Internet]. [cited 2015 Sep 20]. Available from: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=133269

53. Hussain SM, Outwater EK, Siegelman ES. Mucinous versus Nonmucinous Rectal Carcinomas: Differentiation with MR Imaging. Radiology. 1999 Oct 1;213(1):79–85.

54. Hussain SM, Outwater EK, Siegelman ES. MR imaging features of pelvic mucinous carcinomas. Eur Radiol. 2000;10(6):885–91.

55. Kim MJ, Huh YM, Park YN, Kim NK, Kim DJ, Chung JJ, et al. Colorectal mucinous carcinoma: findings on MRI. J Comput Assist Tomogr. 1999 Apr;23(2):291–6.

56. Rectal Carcinoma Staging: A Practical Approach [Internet]. [cited 2015 Sep 20]. Available from: http://www.researchgate.net/publication/266108623_Rectal_Carcinoma_Staging_A_Practical_Approach

57. Taylor FGM, Swift RI, Blomqvist L, Brown G. A systematic approach to the interpretation of preoperative staging MRI for rectal cancer. AJR Am J Roentgenol. 2008 Dec;191(6):1827–35.

58. Willett CG, Badizadegan K, Ancukiewicz M, Shellito PC. Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? Dis Colon Rectum. 1999 Feb;42(2):167–73.

59. Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. The prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorectal Dis. 2001 Sep;16(5):298–304.

60. Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. Br J Surg. 2008 Feb;95(2):229–36.

61. Shihab OC, Moran BJ, Heald RJ, Quirke P, Brown G. MRI staging of low rectal cancer. Eur Radiol. 2009 Mar;19(3):643–50.

62. Rociu E, Stoker J, Zwamborn AW, Laméris JS. Endoanal MR imaging of the anal sphincter in fecal incontinence. Radiogr Rev Publ Radiol Soc N Am Inc. 1999 Oct;19 Spec No:S171–7.

63. Matsuoka H, Masaki T, Sugiyama M, Nakamura A, Takahara T, Hachiya J, et al. Gadolinium enhanced endorectal coil and air enema magnetic resonance imaging as a useful tool in the preoperative examination of patients with rectal carcinoma. Hepatogastroenterology. 2004 Feb;51(55):131–5.

64. Koh D-M, Chau I, Tait D, Wotherspoon A, Cunningham D, Brown G. Evaluating mesorectal lymph nodes in rectal cancer before and after neoadjuvant chemoradiation using

thin-section T2-weighted magnetic resonance imaging. Int J Radiat Oncol Biol Phys. 2008 Jun 1;71(2):456–61.

65. Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, Dallimore NS, et al. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology. 2003 May;227(2):371–7.

66. Matsuoka H, Nakamura A, Sugiyama M, Hachiya J, Atomi Y, Masaki T. MRI diagnosis of mesorectal lymph node metastasis in patients with rectal carcinoma. what is the optimal criterion? Anticancer Res. 2004 Dec;24(6):4097–101.

67. Kim JH, Beets GL, Kim M-J, Kessels AGH, Beets-Tan RGH. High-resolution MR imaging for nodal staging in rectal cancer: are there any criteria in addition to the size? Eur J Radiol. 2004 Oct;52(1):78–83.

68. colonmedium.pdf [Internet]. [cited 2015 Sep 20]. Available from: http://cancerstaging.org/references-tools/quickreferences/documents/colonmedium.pdf

69. Jörgren F, Johansson R, Damber L, Lindmark G. Risk factors of rectal cancer local recurrence: population-based survey and validation of the Swedish rectal cancer registry. Colorectal Dis Off J Assoc Coloproctology G B Irel. 2010 Oct;12(10):977–86.

70. Nikberg M, Kindler C, Chabok A, Letocha H, Shetye J, Smedh K. Circumferential resection margin as a prognostic marker in the modern multidisciplinary management of rectal cancer. Dis Colon Rectum. 2015 Mar;58(3):275–82.

71. Patel UB, Brown G, Rutten H, West N, Sebag-Montefiore D, Glynne-Jones R, et al. Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer. Ann Surg Oncol. 2012 Sep;19(9):2842–52.

72. Rullier A, Laurent C, Vendrely V, Le Bail B, Bioulac-Sage P, Rullier E. Impact of colloid response on survival after preoperative radiotherapy in locally advanced rectal carcinoma. Am J Surg Pathol. 2005 May;29(5):602–6.

73. Shia J, Guillem JG, Moore HG, Tickoo SK, Qin J, Ruo L, et al. Patterns of morphologic alteration in residual rectal carcinoma following preoperative chemoradiation and their association with long-term outcome. Am J Surg Pathol. 2004 Feb;28(2):215–23.

74. Shia J, McManus M, Guillem JG, Leibold T, Zhou Q, Tang LH, et al. Significance of acellular mucin pools in rectal carcinoma after neoadjuvant chemoradiotherapy. Am J Surg Pathol. 2011 Jan;35(1):127–34.

75. Kulkarni T, Gollins S, Maw A, Hobson P, Byrne R, Widdowson D. Magnetic resonance imaging in rectal cancer downstaged using neoadjuvant chemoradiation: accuracy of prediction of tumour stage and circumferential resection margin status. Colorectal Dis Off J Assoc Coloproctology G B Irel. 2008 Jun;10(5):479–89.

76. Suppiah A, Hunter IA, Cowley J, Garimella V, Cast J, Hartley JE, et al. Magnetic resonance imaging accuracy in assessing tumour down-staging following chemoradiation in rectal cancer. Colorectal Dis Off J Assoc Coloproctology G B Irel. 2009 Mar;11(3):249–53.

77. Kim DJ, Kim JH, Lim JS, Yu J-S, Chung J-J, Kim M-J, et al. Restaging of Rectal Cancer with MR Imaging after Concurrent Chemotherapy and Radiation Therapy. Radiogr Rev Publ Radiol Soc N Am Inc. 2010 Mar;30(2):503–16.

78. Kuo L-J, Chern M-C, Tsou M-H, Liu M-C, Jian JJ-M, Chen C-M, et al. Interpretation of magnetic resonance imaging for locally advanced rectal carcinoma after preoperative chemoradiation therapy. Dis Colon Rectum. 2005 Jan;48(1):23–8.

79. De Nardi P, Carvello M. How reliable is current imaging in restaging rectal cancer after neoadjuvant therapy? World J Gastroenterol WJG. 2013 Sep 28;19(36):5964–72.

80. Significance of MRI-assessed tumor response for locally advanced rectal cancer treated with preoperative long-course chemoradiation: Kuwait Cancer Control Center experience. | 2014 ASCO Annual Meeting | Abstracts | Meeting Library [Internet]. [cited 2015 Sep 22]. Available from: http://meetinglibrary.asco.org/content/130806-144

81. Shihab OC, Taylor F, Salerno G, Heald RJ, Quirke P, Moran BJ, et al. MRI predictive factors for long-term outcomes of low rectal tumours. Ann Surg Oncol. 2011 Nov;18(12):3278–84.

82. Tapan Ü, Özbayrak M, Tatlı S. MRI in local staging of rectal cancer: an update. Diagn Interv Radiol. 2014;20(5):390–8.

83. Rao S-X, Zeng M-S, Chen C-Z, Li R-C, Zhang S-J, Xu J-M, et al. The value of diffusion-weighted imaging in combination with T2-weighted imaging for rectal cancer detection. Eur J Radiol. 2008 Feb;65(2):299–303.

ANNEXURES:

APPENDIX (1)

Ser no: **RECTAL CANCER STUDY:**

Name: Hosp no:

Age:

Age groups:
<25 years = 1
26-40 years =2
>40 years = 3

Gender: Female = 0
Male = 1

Histopathology:
Type: Adenocarcinoma =1
Mucinous adenocarcinoma = 2
Signet ring cell carcinoma = 3
Others = 4

Histological grading:
Well differentiated =1
Moderately differentiated =2
Poorly differentiated =3
Undifferentiated = 4

Grading:
Low grade (well and moderately differentiated) = 1
High grade (Poorly differentiated and undifferentiated) = 2

Type of neoadjuvant chemotherapy:
Short course chemoradiation = 1
Long course chemoradiation = 2
Radical chemoradiation = 3
Chemotherapy = 4

Concomitant chemotherapy administered: Yes= 1
No = 0

Dose of RT administered:

Time interval between last treatment and imaging: (in weeks)
≥ 6weeks = 1
6-8 weeks = 2
8-10 weeks = 3
>10 weeks = 4

Pretreatment MRI

Type:
Circumferential = 1
Hemicircumferential = 2
Polypoid = 3

Location:

High	**Yes=1**	
	No =0	
Mid	**Yes =1**	
	No = 0	
Low	**Yes=1**	
	No = 0	

If the tumor location is low,

Involvement of puborectalis, Yes= 1
No = 0

Involvement of the following structures, if low lying tumor,
Internal anal sphincter , Yes = 1
No = 0

External anal sphincter, Yes = 1
No =0

Ischiorectal fossa, Yes = 1
No =0

Invasion of adjacent structures, Yes =1
No =0

		Pre treatment MRI	Post treatment MRI
Length (cm)			
Width (cm)			
Distance from anal verge (cm)			
CRM		**Present (>2mm) = 1**	**Present (>2mm) = 1**
		Absent (<2mm) = 0	**Absent (<2mm) = 0**
CRM (mm)			
T2 signal intensity	**High signal = 1**		
	Intermediate signal = 2		
	Low signal = 3		
T stage	**T1 = 1**		
	T2 = 2		
	T3 = 3		
	T4 = 4		
T3 stage	**T3 a = 1**		
	T3b = 2		
	T3c = 3		
	T3d = 4		
N stage	**N0 = 0**		
	N1 = 1		
	N2 = 2		
EMVI	**Yes = 1**		
	No = 0		

M stage	**Yes = 1**		
	No = 0		
Stage	**Stage 1 = 1**		
	Stage 2 = 2		
	Stage 3 = 3		
	Stage 4 = 4		
MRI TRG	**1**	----	
	2		
	3		
	4		
	5		

APPENDIX (2):

Department of Radiodiagnosis, Christian Medical College, Vellore

CONSENT TO TAKE PART IN RECTAL CANCER STUDY

Study Title:*Comparison of response to neoadjuvant therapy using MRI tumor regression grading in patients with carcinoma rectum below 25 years of age and above 25 years of age*

Study Number:

Patient's name:

Hospital No:

Date of Birth / Age (in years):

I _____

declare that I have read / been read to the information sheet provided to me regarding this study and have clarified any doubts that I had. [ ]

(Please tick boxes)

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting patient's usual treatment or legal rights [ ]

I understand that study staff and institutional ethics committee will not need my permission to look at patient's health records if I withdraw from the trial. I agree to this access [ ]

I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

I understand that patient's identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

Name:
Signature/thumb impression:
Date:

Name of witness:
Relation to participant:
Date:

Department of Radiodiagnosis, Christian Medical College, Vellore

Study Title:*Comparison of response to neoadjuvant therapy using MRI tumor regression grading in patients with carcinoma rectum below 25 years of age and above 25 years of age*

PATIENT INFORMATION SHEET:

You are being requested to participate in a study to assess the response to neoadjuavnt therapy for rectal cancer using MRI grading. At present, those patients with rectal cancer who undergo neoadjuvant therapy routinely have a second MRI after completing the treatment to assess the response to treatment. We hope to find out whether the response to neoadjuvant treatment in the age group below 25 years of age is different from the age group above 25 years of age with the help of MRI findings..

What additional tests do I have to go through if I take part in this study?

If you take part in this study, your MRI scan will be done as a routine test by the primary investigator as prescribed by your clinician. You will not have to pay any additional amount.

Does MRI scan have any side effects?

MRI scan does not have any harmful radiation. We will be doing it the same way as you would have it if you were not included in this study.

If I take part in this study, what will I have to do?

If you agree to participate in this study, there will be no change in the other investigations and treatment that you will be receiving. You will be expected to come for the MRI scan as advised by your doctor. No additional blood tests will be done as a part of this study.

Can I withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if I develop any study related injury?

This scan does not involve harmful radiation and it is non- invasive. So, we do not expect any major procedure related injury. However you can immediately report to us.

Will I have to pay for the additional tests?

MRI scan is usually done as a part of your routine tests. You will not have to pay any additional amount than that is required. All other investigations, as requested by your

doctor will continue in the usual manner. How much you pay for these investigations will not change and this has nothing to do with your participation in this study.

What happens after the study is over?

You may or may not benefit from this study. Once the study is over, we will analyze the results and come to a conclusion and we will be able to use these results and find out whether patients with rectal cancer below 25 years of age respond differently to neoadjuvant therpay compared to patients above 25 years of age.

Will my personal details be kept confidential?

The results of this study will/may be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical record **may** be reviewed by doctors associated with the study, without your additional permission.

If you have any further questions, please contact Dr Shibi Paul(Tel: 0416 228-3012/2027/3609) between 8am & 4:30pm from Monday to Friday and from 8am to 12:30pm on Saturday or you can email your queries to shibipaul13@gmail.com .

APPENDIX (3):

MASTER TABLE

ID	HOSPI	AGE	SEX	HISTO	GRADE	NEORX	CHEMO	RTDOSE	TIME	TYPE	LOCN	HI	MID	LOW	PBREC	IAS	EAS	IRF	ADJ
1	104455f	42	1	3	3	2	1	5040	1	1	3	0	0	1	F	T	F	F	F
2	111464f	33	1	1	2	2	1	5040	2	2	3	0	0	1	F	T	F	F	F
3	026145f	32	1	2	1	2	1	5040	1	1	3	0	1	1	T	T	F	F	T
4	119193f	35	1	1	2	2	1	5040	1	2	2	1	1	0	F	F	F	F	F
5	125228f	42	1	1	2	2	1	5040	2	1	3	0	0	1	T	T	F	F	F
6	123375f	46	0	1	2	2	1	5040	2	1	2	1	1	0	F	F	F	F	F
7	132034f	42	1	3	3	2	1	5040	1	1	3	0	1	1	F	F	F	F	F
8	119193f	35	1	1	2	2	1	5040	1	3	2	1	1	0	F	F	F	F	F
9	506652d	43	1	1	1	2	1	5040	1	1	3	0	1	1	F	F	F	F	F
10	428039	72	1	1	2	2	1	5040	1	1	3	0	0	1	T	F	F	F	F
11	175137f	68	1	1	2	1	1	5040	2	1	3	1	1	1	F	F	F	F	T
12	173122f	33	1	1	3	2	1	5040	2	1	3	0	0	1	F	F	F	F	F
13	182633f	61	0	1	3	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
14	178661f	35	1	1	2	2	1	5040	2	3	2	0	1	0	F	F	F	F	F
15	108200f	27	1	1	2	2	1	5040	3	1	1	1	0	0	F	F	F	F	F
16	031803f	69	1	1	3	2	1	5040	2	3	2	1	1	0	F	F	F	F	F
17	201892f	58	0	1	2	2	1	5040	3	1	3	0	0	1	F	F	F	F	T
18	208919f	39	0	1	2	2	1	5040	1	1	3	0	0	1	T	T	F	F	T
19	229471f	55	1	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
20	264554f	32	1	2		2	1	5040	2	1	3	1	1	1	F	F	F	F	F
21	251059f	33	0	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
22	276207f	60	0	1	2	2	1	5040	2	1	2	0	1	0	F	F	F	F	F
23	283177f	36	1	1	2	2	1	5040	1	2	3	0	0	1	F	F	F	F	F
24	286035f	53	0	1	2	2	1	5040	1	1	3	0	0	1	F	F	F	F	F
25	293908f	76	1	1	2	2	1	5040	1	3	1	1	0	0	F	F	F	F	F
26	303908f	63	1	1	2	2	1	5040	1	2	2	0	1	0	F	F	F	F	F
27	303406f	68	0	1	2	2	1	5040	1	1	3	3	0	1	T	F	F	F	F

56	706751f	63	1	1	2	4			1	1	3	1	1	1	T	F	F	F	F
57	682202f	22	0	1	2	2	1	5040	1		3	2	0	1	F	F	F	F	F
58	723468f	38	0	1		2	1	5040	1	1	3	0	0	1	T	T	T	F	F
59	728434f	58	0	2		2	1	5040	1	3	1	1	0	0	F	F	F	F	F
60	729376f	48	1	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
61	621947c	81	1	1	2	2	1	5040	1	3	3	0	0	1	F	F	F	F	F
62	767924f	32	1	2		2	1	5040	2	1	2	0	1	0	F	F	F	F	F
63	765355f	68	1	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
64	751274f	59	0	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
65	793698f	45	1	2		4			1	1	2	0	1	0	F	F	F	F	F
66	796426f	40	0	1	2	2	1	5040	1	1	3	0	1	1	F	F	F	F	F
67	803164f	64	1	1	2	4			1	1	3	1	1	1	F	F	F	F	F
68	807038f	63	1	1	2	2	1	5040	1	2	2	0	1	0	F	F	F	F	F
69	802543f	39	1	3	3	2	1	5040	1	1	3	0	1	1	F	F	F	F	F
70	817698f	50	1	1	2	2	1	5040	1	2	3	0	1	1	F	F	F	F	F
71	821087f	59	1	1	2	2	1	5040	1	2	2	1	1	0	F	F	F	F	F
72	641554f	37	1	3	3	2	1	5040	1	1	3	0	0	1	F	F	F	F	F
73	825827f	47	1	3	2	2	1	5040	1	1	1	1	0	0	F	F	F	F	F
74	819889f	67	1	1	2	2	1	5040	1	3	2	1	1	0	F	F	F	F	F
75	834213f	52	1	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
76	841843f	30	1	1	3	2	1	5040	1	1	3	0	0	1	F	F	T	F	F
77	865826f	35	1	1	2	4			1	1	2	0	1	0	F	F	F	F	F
78	851149f	33	1	1	2	2	1	5040	2	1	2	0	1	0	F	F	F	F	F
79	883151f	28	1	3	3	2	1	5040	3	1	2	1	1	0	F	F	F	F	F
80	882620f	49	1	1	3	2	1	5040	1	1	3	1	1	1	F	T	F	F	F
81	895084f	33	0	1	2	2	1	5040	1	3	3	0	0	1	F	F	F	F	F
82	008877g	38	1	3	3	2	1	5040	1	1	3	0	1	1	T	F	F	F	F
83	890183f	17	1	3	3	2	1	5040	1	1	3	0	1	1	T	T	F	F	F

56	706751f	63	1	1	2	4			1	1	3	1	1	1	T	F	F	F	F
57	682202f	22	0	1	2	2	1	5040	1		3	2	0	1	F	F	F	F	F
58	723468f	38	0	1		2	1	5040	1	1	3	0	0	1	T	T	T	F	F
59	728434f	58	0	2		2	1	5040	1	3	1	1	0	0	F	F	F	F	F
60	729376f	48	1	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
61	621947c	81	1	1	2	2	1	5040	1	3	3	0	0	1	F	F	F	F	F
62	767924f	32	1	2		2	1	5040	2	1	2	0	1	0	F	F	F	F	F
63	765355f	68	1	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
64	751274f	59	0	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
65	793698f	45	1	2		4			1	1	2	0	1	0	F	F	F	F	F
66	796426f	40	0	1	2	2	1	5040	1	1	3	0	1	1	F	F	F	F	F
67	803164f	64	1	1	2	4			1	1	3	1	1	1	F	F	F	F	F
68	807038f	63	1	1	2	2	1	5040	1	2	2	0	1	0	F	F	F	F	F
69	802543f	39	1	3	3	2	1	5040	1	1	3	0	1	1	F	F	F	F	F
70	817698f	50	1	1	2	2	1	5040	1	2	3	0	1	1	F	F	F	F	F
71	821087f	59	1	1	2	2	1	5040	1	2	2	1	1	0	F	F	F	F	F
72	641554f	37	1	3	3	2	1	5040	1	1	3	0	0	1	F	F	F	F	F
73	825827f	47	1	3	2	2	1	5040	1	1	1	1	0	0	F	F	F	F	F
74	819889f	67	1	1	2	2	1	5040	1	3	2	1	1	0	F	F	F	F	F
75	834213f	52	1	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
76	841843f	30	1	1	3	2	1	5040	1	1	3	0	0	1	F	F	T	F	F
77	865826f	35	1	1	2	4			1	1	2	0	1	0	F	F	F	F	F
78	851149f	33	1	1	2	2	1	5040	2	1	2	0	1	0	F	F	F	F	F
79	883151f	28	1	3	3	2	1	5040	3	1	2	1	1	0	F	F	F	F	F
80	882620f	49	1	1	3	2	1	5040	1	1	3	1	1	1	F	T	F	F	F
81	895084f	33	0	1	2	2	1	5040	1	3	3	0	0	1	F	F	F	F	F
82	008877g	38	1	3	3	2	1	5040	1	1	3	0	1	1	T	F	F	F	F
83	890183f	17	1	3	3	2	1	5040	1	1	3	0	1	1	T	T	F	F	F

84	011622g	26	1	2		2	1	5040	1	2	2	1	1	0	F	F	F	F	F
85	015949g	56	0	1	2	2	1	5040	1	1	3	1	1	1	F	T	F	F	F
86	036399g	50	1	3	3	4			1	1	3	1	1	1	F	T	F	F	F
87	035436g	33	1	3	3	4			1	1	3	0	1	1	T	T	T	F	F
88	051023g	37	0	1	2	2	1	5040	1	1	3	0	0	1	F	F	F	F	F
89	047391g	31	1	1		2	1	5040	2	1	3	0	0	1	T	T	T	F	F
90	033234g	30	1	1	2	2	1	5040	2	3	3	0	0	1	T	T	F	F	F
91	056366g	58	1	1	2	2	1	5040	2	2	2	1	1	0	F	F	F	F	F
92	082680g	42	1	3	3	2	1	5040	1	1	3	0	0	1	F	T	F	F	F
93	056240g	69	1	1	2	2	1	5040	2	2	3	0	0	1	F	F	F	F	F
94	076742g	49	0	1	2	2	1	5040	1	1	3	0	0	1	F	T	F	F	F
95	267068f	40	0	1	2	2	1	5040	1	3	3	0	0	1	F	T	F	F	F
96	098292g	27	1	1	2	2	1	5040	1	2	3		1	1	F	F	F	F	F
97	068581g	33	1	3	3	2	1	5040	4	1	3	0	1	1	F	F	F	F	F
98	095744g	36	1	1	3	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
99	122456f	53	0	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
100	134407g	45	1	1	2	2	1	5040	1	1	2	0	1	0	F	F	F	F	F
101	128122g	40	1	1	3	4			1	1	3	0	1	1	T	F	T	F	F
102	209587g	47	0	3	3	2	1	5040	2	1	3	0	1	1	F	F	F	F	F
103	156094g	32	0	1	2	2	1	5040	1	1	3	0	0	1	F	F	F	F	F
104	152755g	50	0	1	2	2	1	5040	1	2	3	0	0	1	T	F	F	F	F
105	160610g	44	1	1	2	2	1	5040	1	2	2	1	1	0	F	F	F	F	F
106	164132g	41	1	1		2	1	5040	2	1	2	1	1	0	F	F	F	F	F
107	173784g	39	0	1	2	2	1	5040	1	2	3	0	0	1	F	F	F	F	F
108	174868g	37	1	1	2	2	1	5040	2	1	3	0	1	1	F	F	F	F	F
109	161023g	52	1	1	2	2	1	5040	1	2	3	0	0	1	F	T	F	F	F
110	946543f	33	0	1	2	2	1	5040	1	1	3	0	0	1	F	F	F	F	F
111	598278d	37	0	3	3	2	1	5040	2	2	2	0	1	0	F	F	F	F	F

112	199776g	30	1	1	3	2	1	5040	1	1	3	0	1	1	T	F	F	F	F
113	203741g	50	1	1	2	2	1	5040	1	3	3	0	0	1	F	T	F	F	F
114	191348g	58	1	1	2	2	1	5040	1	1	3	0	1	1	F	F	F	F	F
115	206101g	31	1	1	2	2	1	5040	2	1	3	0	1	1	F	F	F	F	F
116	207926g	40	1	1	3	2	1	5040	2	3	2	0	1	0	F	F	F	F	F
117	226317g	32	1	3	3	2	1	5040	1	1	3	0	1	1	F	F	F	F	F
118	499972f	22	0	3	3	2	1	5040	1	3	2	0	1	0	F	F	F	F	F
119	496467f	24	0	3	3	4			1	1	1	1	1	1	T	F	F	F	F
120	601090f	24	1	1	2	2	1	5040	1	1	2	1	1	0	F	F	F	F	F
121	042071g	23	0	1	2	2	1	5040	3	2	3	0	0	1	F	T	F	F	F
122	335922f	20	1	2		2	1	5040	1	3	3	0	0	1	F	F	F	F	F
123	357562f	19	1	2	3	4			1	1	3	1	1	1	T	F	F	F	F
124	142308f	24	0	1	2	2	1	5040	1	1	2	0	1	0	F	F	F	F	F
125	380665f	22	0	1	2	4			1	1	3	0	0	1	T	F	F	F	T
126	140644g	25	1	1	2	2	1	5040	1	1	2	0	1	0	F	F	F	F	F
127	774839f	25	0	1	2	2	1	5040	1	1	3	0	1	1	F	F	F	F	F
128	780237f	23	0	1	2	2	1	5040	1	1	1	0	1	1	T	F	F	F	F
129	806825f	23	0	2		2	1	5040	1	1	1	0	1	1	T	F	F	F	F
130	833441f	25	1	3	3	2	1	5040	1	2	1	0	1	1	T	T	F	F	F
131	189560g	22	1	3	3	2	1	5040	1	2	1	0	1	1	F	F	F	F	F
132	163445g	24	0	1	1	2	1	5040	1	1	3	0	0	1	F	F	F	F	F
133	140374g	21	0	1	3	2	1	5040	1	1	3	0	1	1	T	T	F	F	F
134	779234f	21	1	1	2	2	1	5040	1	1	3	0	0	1	T	F	F	F	F
135	887876f	21	1	1	2	2	1	5040	1	3	3	0	0	1	F	F	F	F	F
136	888452f	19	0	1	2	2	1	5040	2	1	2	1	1	0	F	F	F	F	F
137	287766f	24	1	1	2	2	1	5040	1	1	3	0	1	1	F	F	F	F	F
138	300302f	22	1	1	2	2	1	5040	2	3	3	0	0	1	F	F	F	F	F
139	067487f	20	1	3	3	2	1	5040	1	1	2	0	1	0	F	F	F	F	F

140	845860d	20	1	1	2	2	1	5040	2	3	3	0	0	1	T	F	F	F	T
141	037234f	22	1	3	3	2	1	5040	3	1	2	1	1	0	F	F	F	F	F
142	387301f	23	1	1	2	4			1	3	2	1	1	0	F	F	F	F	F

ID	HOSPI	LEN 1	LEN 2	DIST 1	DIST 1	CRM 1	CRM 2	T2SI G	TS 1	TS 2	T3S 1	T3S 2	NPR E	NPOS T	EM 1	EM 2	MPR E	MPOS T	STG 1	STG 2	TR G
1	104455 f	5.2	1.8	0	2.5	0	1	2	3	2	2		1	0	0	0	0	0	3	1	2
2	111464 f	5.4	1.6	0	0	0	1	2	3	2	2		1	0	0	0	0	0	3	1	2
3	026145 f	9.3	7	0	2.6	0	0	1	4	3		4	1	0	0	0	0	0	3	2	5
4	119193 f	8.8	5.9	5.2	5.3	0	0	2	3	3	4	2	2	2	1	1	0	0	3	3	3
5	125228 f	5.5	5.1	0	0	0	0	2	3	3	3	3	1	0	0	0	0	0	3	2	3
6	123375 f	6.3	5.6	3.2	5.5	1	1	2	3	3	1	1	1	1	0	1	0	0	3	3	4
7	132034 f	8	7.8	0	0	0	0	1	3	3	4	4	2	2	1	1	0	0	3	3	5
8	119193 f	8.4	7.9	3.9	4.5	0	0	2	3	3	3	2	2	1	1	0	0	0	3	3	3
9	506652 d	7.8	6.5	0	0	0	0	2	3	2	3		1	0	0	0	0	0	3	1	2
10	428039	4	3.7	2	3	1	1	2	3	3	3	2	0	0	0	0	0	0	2	2	4

11	175137 f	7.1	5.8	2.2	2.8	0	0	2	4	3		2	2	1	0	0	0	0	3	3	1
12	173122 f	7.9	6.9	1.5	2.5	0	0	2	3	4	4		2	2	1	1	0	0	3	3	5
13	182633 f	9.9	5.7	3.8	4.6	0	1	2	3	3	3	2	2	1	1	0	0	0	3	3	1
14	178661 f	5.8	3.9	5	5.2	0	0	2	3	3	3	2	2	1	0	0	0	0	3	3	3
15	108200 f	3.4	2.5	7.8	8	1	1	2	3	3	3	3	1	0	0	0	0	0	3	2	3
16	031803 f	4.9	3.4	5.6	7	0	0	2	3	3	4	2	2	1	0	0	0	0	3	3	3
17	201892 f	4.5	4	0	0	0	0	2	4	4			2	0	0	0	0	0	3	2	3
18	208919 f	4	3.3	2.3	2.5	0	1	2	4	3		2	1	0	0	0	0	0	3	2	3
19	229471 f	6.9	5.9	4.9	5.2	0	1	2	3	3	4	2	2	1	1	0	0	0	3	3	2
20	264554 f	9.4	8.8	4.6	4.8	0	0	1	3	3	3	3	2	2	1	1	0	0	3	3	4
21	251059 f	8.2	8	7.8	7.6	0	0	1	4	4			2	2	1	1	0	0	3	3	4
22	276207 f	4	2.4	8	8.4	1	1	2	3	3	3	2	1	1	0	0	0	0	3	3	2
23	283177 f	4.9	2	4.3	5.2	0	1	2	3	3	3	2	2	1	0	0	0	0	3	3	3
24	286035 f	4.7	3.8	4.2	4.4			2	3	3	3	3	1	1	1	1	0	0	3	3	4
25	293908 f	7.9	6.1	8.9	9	0		2	4	4			2	1	1	1	0	0	3	3	4
26	303908 f	8	4	5.8	5.9	1	1		3	2	3		2	1	0	0	0	0	3	3	2

27	303406 f	10.6	10.1	2	2.6	0	0	2	3	3	2	2	1	0	0	0	0	0	3	2	4
28	326007 f	9.5	9.5	3	3	0	1	1	3	3	4	3	2	0	0	0	0	0	3	2	4
29	355793 f	7.3	5.6	3.5	3.7	0	0	2	4	3		3	2	1	0	0	0	0	3	3	3
30	350252 f	4.2	3.1	1.8	2.6	0	0	2	4	4			2	1	1	0	1	1	4	4	4
31	369200 f	5.4	5.2	3.2	3.9	0	0	2	3	3	3	3	1	1	0	0	0	0	3	3	4
32	368817 f	5.3	4.1	1.3	2.1	0	0	2	3	3	3	2	1	0	0	0	0	0	3	2	3
33	382965 f	7	5.5	1.7	2.2	0	0	1	4	3		3	2	0	0	0	0	0	3	3	4
34	377076 f	9.5	13	3.4	2.8	0	0	1	4	4			2	2	1	1	0	0	3	3	5
35	992085 c	8.3	6.2	1	1.3	0	0	2	3	3	4	4	2	2	1	1	0	0	3	3	4
36	432183 f	4.8	3.5	3.9	4.4	0	0	2	3	3	3	2	2	0	1	0	0	0	3	2	3
37	449348 f	6	4.7	1.3	2	0	0	2	3	3	3	2	2	0	1	0	0	0	3	2	2
38	451446 f	6.6	4.5	1.3	1.9	0	0	2	3	3	3	2	2	1	1	0	0	0	3	3	3
39	468398 f	5	4.2	0	0	0	0	2	3	3	3	1	2	0	0	0	0	0	3	2	4
40	453685 f	5.4	4.8	0	1	0	0	1	3	3	2	1	0	0	0	0	0	0	2	2	4
41	472681 f	2.2	1.8	0.8	1.2	0	0	2	3	3	2	1	1	0	0	0	0	0	3	2	3
42	477345 f	6	5	3	4	0	0	2	4	4			2	2	1	1	0	0	3	3	4

59	728434 f	5.2	3.3	12	14	0	0	2	4	4			0	0	0	0	0	0	2	2	4
60	729376 f	8.6	6.3	5.2	5.5	0	0	2	3	3	4	4	2	1	1	1	0	0	3	3	4
61	621947 c	3.6	3.3	0.9	1	0	0	2	3	3	3	3	2	0	1	0	0	0	3	2	4
62	767924 f	6.2	4	2.8	3.2	0	1	2	3	2	2		2	0	0	0	0	0	3	1	2
63	765355 f	7	6	5.1	6.2	0	0	2	4	3		3	2	1	0	1	0	0	3	3	4
64	751274 f	8.3	5.3	3.6	5.1	0	0	2	4	4			2	0	0	0	0	0	3	2	3
65	793698 f	5.2	3.4	3.4	4.8	0	0	1	3	3	3	3	2	2	1	1	0	0	3	3	3
66	796426 f	4.7	3.9	3.5	5.7	0	0	2	3	3	3	2	2	2	0	0	0	0	3	3	4
67	803164 f	7.7	5.5	1.9	1.5	0	0	2	4	4			2	1	1	1	0	0	3	3	5
68	807038 f	3.3	2.7	3.2	3.4	1	1	2	3	3	2	1	0	0	0	0	0	0	2	2	3
69	802543 f	11	10.3	0	0	0	0	2	4	4			2	2	1	1	0	0	3	3	4
70	817698 f	6	4	0	1	0	0	3	3	2	2		2	0	1	0	0	0	3	1	2
71	821087 f	7.2	6.7	4.3	4.6	0	0	2	3	3	2	1	2	1	0	0	0	0	3	3	3
72	641554 f	10.9	10.9	2.4	2.4	0	0	1	3	3	3	3	2	2	0	0	0	0	3	3	5
73	825827 f	6.2	3.5	6.4	6.8	0	1	1	3	3	3	2	2	0	0	0	0	0	3	2	3
74	819889 f	6.2	4.3	4.5	6.1	0	1	2	3	2	2		2	0	0	0	0	0	3	2	2

59	728434 f	5.2	3.3	12	14	0	0	2	4	4			0	0	0	0	0	0	2	2	4
60	729376 f	8.6	6.3	5.2	5.5	0	0	2	3	3	4	4	2	1	1	1	0	0	3	3	4
61	621947 c	3.6	3.3	0.9	1	0	0	2	3	3	3	3	2	0	1	0	0	0	3	2	4
62	767924 f	6.2	4	2.8	3.2	0	1	2	3	2	2		2	0	0	0	0	0	3	1	2
63	765355 f	7	6	5.1	6.2	0	0	2	4	3		3	2	1	0	1	0	0	3	3	4
64	751274 f	8.3	5.3	3.6	5.1	0	0	2	4	4			2	0	0	0	0	0	3	2	3
65	793698 f	5.2	3.4	3.4	4.8	0	0	1	3	3	3	3	2	2	1	1	0	0	3	3	3
66	796426 f	4.7	3.9	3.5	5.7	0	0	2	3	3	3	2	2	2	0	0	0	0	3	3	4
67	803164 f	7.7	5.5	1.9	1.5	0	0	2	4	4			2	1	1	1	0	0	3	3	5
68	807038 f	3.3	2.7	3.2	3.4	1	1	2	3	3	2	1	0	0	0	0	0	0	2	2	3
69	802543 f	11	10.3	0	0	0	0	2	4	4			2	2	1	1	0	0	3	3	4
70	817698 f	6	4	0	1	0	0	3	3	2	2		2	0	1	0	0	0	3	1	2
71	821087 f	7.2	6.7	4.3	4.6	0	0	2	3	3	2	1	2	1	0	0	0	0	3	3	3
72	641554 f	10.9	10.9	2.4	2.4	0	0	1	3	3	3	3	2	2	0	0	0	0	3	3	5
73	825827 f	6.2	3.5	6.4	6.8	0	1	1	3	3	3	2	2	0	0	0	0	0	3	2	3
74	819889 f	6.2	4.3	4.5	6.1	0	1	2	3	2	2		2	0	0	0	0	0	3	2	2

43	483456 f	6.4	5.5	3.7	4	0	0	2	3	3	4	4	2	0	1	1	0	0	3	2	4
44	499490 f	5.7	4	0	0	0	0	2	3	3	3	2	0	0	1	0	0	0	3	2	3
45	600790 f	3.7	3.5	1.5	3	0	0	2	3	3	3	2	1	0	0	0	0	0	3	2	3
46	605306 f	5.2	4.1	1.2	1.5	0	0	2	3	3	3	2	2	2	1	1	0	0	3	3	3
47	293797 b	3.9	2	1.8	2	0	0	2	3	3	2	0	1	0	0	0	0	0	3	2	2
48	631162 f	3.4	3	0	0	0	0	2	3	3	4	3	1	0	0	0	0	0	3	2	3
49	714835 f	3.9	3.8	0	0	0	0	2	3	3	3	2	2	1	0	0	0	0	3	3	3
50	642430 f	10.2	6.3	3	5	0	0	2	3	2	3		2	0	0	0	0	0	3	1	2
51	641563 f	5.3	2.5	2.2	3.5	1	1	2	3	3	3	2	1	0	1	0	0	0	3	2	2
52	659010 f	3.3	2	7.6	8.6	0	0	3	4	3		1	1	0	0	0	0	0	3	2	3
53	641554 f	10.9	10.9	10.9	2.4	0	0	1	3	3	3	3	2	2	0	0	0	0	3	3	5
54	658056 f	9.5	8.2	0	0	0	1	2	3	3	2	1	1	0	0	0	0	0	3	2	3
55	686194 f	3.9	3.2	3.3	3	0	1	2	3	3	3	2	1	0	0	0	0	0	3	2	4
56	706751 f	8.8	4.7	1.3	2.6	0	0	2	4	3		2	2	1	0	0	0	0	3	3	3
57	682202 f	7.4	5.2	0.8	7.5	0	0	2	3	3	3	1	2	0	0	0	0	0	3	2	3
58	723468 f	4.6	4.5	0	0	0	0	1	4	3		3	1	1	0	0	0	0	3	3	5

43	483456 f	6.4	5.5	3.7	4	0	0	2	3	3	4	4	2	0	1	1	0	0	3	2	4
44	499490 f	5.7	4	0	0	0	0	2	3	3	3	2	0	0	1	0	0	0	3	2	3
45	600790 f	3.7	3.5	1.5	3	0	0	2	3	3	3	2	1	0	0	0	0	0	3	2	3
46	605306 f	5.2	4.1	1.2	1.5	0	0	2	3	3	3	2	2	2	1	1	0	0	3	3	3
47	293797 b	3.9	2	1.8	2	0	0	2	3	3	2	0	1	0	0	0	0	0	3	2	2
48	631162 f	3.4	3	0	0	0	0	2	3	3	4	3	1	0	0	0	0	0	3	2	3
49	714835 f	3.9	3.8	0	0	0	0	2	3	3	3	2	2	1	0	0	0	0	3	3	3
50	642430 f	10.2	6.3	3	5	0	0	2	3	2	3		2	0	0	0	0	0	3	1	2
51	641563 f	5.3	2.5	2.2	3.5	1	1	2	3	3	3	2	1	0	1	0	0	0	3	2	2
52	659010 f	3.3	2	7.6	8.6	0	0	3	4	3		1	1	0	0	0	0	0	3	2	3
53	641554 f	10.9	10.9	10.9	2.4	0	0	1	3	3	3	3	2	2	0	0	0	0	3	3	5
54	658056 f	9.5	8.2	0	0	0	1	2	3	3	2	1	1	0	0	0	0	0	3	2	3
55	686194 f	3.9	3.2	3.3	3	0	1	2	3	3	3	2	1	0	0	0	0	0	3	2	4
56	706751 f	8.8	4.7	1.3	2.6	0	0	2	4	3		2	2	1	0	0	0	0	3	3	3
57	682202 f	7.4	5.2	0.8	7.5	0	0	2	3	3	3	1	2	0	0	0	0	0	3	2	3
58	723468 f	4.6	4.5	0	0	0	0	1	4	3		3	1	1	0	0	0	0	3	3	5

75	834213 f	8.5	8.2	2	2.3	0	0	2	4	4			2	1	1	1	0	0	3	3	4
76	841843 f	7.5	5.6	0	0	0	0	2	3	3	4	2	2	2	1	0	0	0	3	3	3
77	865826 f	6.9	5.3	3.8	4.2	0	0	1	3	3	3	3	2	2	1	0	1	1	4	4	3
78	851149 f	6	5.5	4	4.4	1	1	2	3	3	3	2	2	1	0	0	0	0	3	3	2
79	883151 f	9.5	7	4	4.5	0	0	3	3	3	3	2	2	1	0	0	0	0	3	3	2
80	882620 f	6.9	5.5	0	0	0	0	3	3	3	3	2	2	1	1	0	0	0	3	3	3
81	895084 f	5.9	4.4	0	2.4	0	0	3	2	2			2	0	0	0	0	0	3	1	3
82	008877 g	5.5	5.1	0	0	0	0	2	3	3	3	3	2	2	0	0	0	0	3	3	2
83	890183 f	7.6	7.3	0	0	0	0	1	3	3	3	3	2	2	1	1	0	0	3	3	4
84	011622 g	10	5	6.6	7.2	0	0	2	3	3	4	3	2	2	1	0	0	0	3	3	3
85	015949 g	11.2	8.5	3	4	0	0	2	4	4			2	2	1	1	0	0	3	3	5
86	036399 g	13	10.5	0	0	0	0	1	3	3	3	3	2	2	1	1	1	1	4	4	5
87	035436 g	10.8	10.2	0	0	0	0	1	4	4			2	2	1	1	1	1	4	4	5
88	051023 g	7.9	5.8	0	0	0	0	2	4	4			2	0	0	0	0	0	3	2	3
89	047391 g	6.5	4.7	0	0	0	0	2	4	4			2	0	0	0	0	0	3	2	4
90	033234 g	7.7	6	0	0	0	0	1	4	3		4	2	2	1	1	0	0	3	3	4

91	056366 g	6	5.1	5	5.9	0	0	2	4	3		3	1	1	1	0	0	0	3	3	3
92	082680 g	8.3	8.3	0	0	0	0	3	3	3	3	3	1	0	1	1	0	0	3	2	5
93	056240 g	4.7	2	0	0	0	0	2	3	3	2	1	1	0	0	0	0	0	3	2	3
94	076742 g	4.6	3.9	0	0	0	0	2	2	2			2	0	0	0	0	0	3	2	4
95	267068 f	4.3	1.6	0	0	0	0	2	2	1			1	0	0	0	0	0	3	1	2
96	098292 g	4.1	2.3	0	0	0	1	2	3	2	2		2	0	0	0	0	0	3	1	2
97	068581 g	7.4	7.3	0	0	0	0	1	3	3	3	3	2	2	1	1	0	0	3	3	4
98	095744 g	9.7	8.7	2.2	2.4	0	0	2	4	3		4	2	1	1	1	0	0	3	3	4
99	122456 f	4.3	3.2	4.4	5.8	0	1	2	3	3	3	2	2	2	1	1	0	0	3	3	3
100	134407 g	5.9	2.6	6.5	7	0	0	2	3	2	2		2	0	1	0	0	0	3	1	2
101	128122 g	7.6	7.6	0	0	0	0	1	4	4			2	2	1	1	0	0	3	3	5
102	209587 g	6.5	6	0.9	1.8	0	0	2	3	3	4	3	2	1	1	1	0	0	3	3	4
103	156094 g	7.5	4	0	0	0	0	2	3	3	4	3	2	1	1	1	0	0	3	3	3
104	152755 g	5.7	4.8	0	0	0	0	2	3	3	4	2	2	1	0	0	0	0	3	3	3
105	160610 g	6.6	6	2.5	3.2	1	1	1	3	3	3	2	2	0	1	0	0	0	3	3	3
106	164132 g	8.7	6.9	4.6	4.6	0	0	2	3	4	4		2	1	1	0	0	0	3	3	3

107	173784g	6.8	4.4	0	0	0	0	2	2	2			1	0	0	0	0	0	3	1	3
108	174868g	4.7	3.1	1.2	1.8	0	0	2	3	3	3	3	2	1	0	0	0	0	3	3	3
109	161023g	4	3.4	0	0	0	0	2	3	3	3	2	2	2	1	0	0	0	3	3	3
110	946543f	3.7	3.5	0	0.6	0	0	2	3	4	3		2	0	1	1	0	0	3	2	4
111	598278d	6	5	3.7	3.8	0	0	2	3	3	3	2	2	2	1	1	0	0	3	3	4
112	199776g	8.2	7.3	0	2.1	0	0	2	3	3	4	3	2	1	1	1	0	0	3	3	3
113	203741g	8.3	7.4	0	0	0	0	2	2	2			2	0	0	0	0	0	3	1	3
114	191348g	5.4	3.6	2	3.8	0	1	2	3	3	4	2	2	2	1	1	0	0	3	3	3
115	206101g	5.4	3.8	2.4	3.7	1	1	1	3	3	2	2	2	0	0	0	0	0	3	2	3
116	207926g	4.6	2.1	1.4	71.1	1	0	2	2	2			2	0	0	0	0	0	3	1	4
117	226317g	5.4	5.1	3.1	3.7	0	0	1	4	4			2	2	1	1	0	0	3	3	5
118	499972f	4.6	4.5	3.5	3.9	0	0	1	3	3	2	2	2	2	0	0	0	0	3	3	4
119	496467f	11	11	0	0	0	0	1	3	4	3		2	2	0	0	0	1	3	4	5
120	601090f	6.6	3.8	2.2	1.1	0	0	2	3	3	4	3	1	0	0	0	0	0	3	2	2
121	042071g	6.3	5.4	0	0	0	0	2	3	3	3	1	2	1	1	0	0	0	3	3	4
122	335922f	1.5	1.2	0	0	1	1	1	2	2			2	2	0	0	0	0	3	3	1

107	173784g	6.8	4.4	0	0	0	0	2	2	2			1	0	0	0	0	0	3	1	3
108	174868g	4.7	3.1	1.2	1.8	0	0	2	3	3	3	3	2	1	0	0	0	0	3	3	3
109	161023g	4	3.4	0	0	0	0	2	3	3	3	2	2	2	1	0	0	0	3	3	3
110	946543f	3.7	3.5	0	0.6	0	0	2	3	4	3		2	0	1	1	0	0	3	2	4
111	598278d	6	5	3.7	3.8	0	0	2	3	3	3	2	2	2	1	1	0	0	3	3	4
112	199776g	8.2	7.3	0	2.1	0	0	2	3	3	4	3	2	1	1	1	0	0	3	3	3
113	203741g	8.3	7.4	0	0	0	0	2	2	2			2	0	0	0	0	0	3	1	3
114	191348g	5.4	3.6	2	3.8	0	1	2	3	3	4	2	2	2	1	1	0	0	3	3	3
115	206101g	5.4	3.8	2.4	3.7	1	1	1	3	3	2	2	2	0	0	0	0	0	3	2	3
116	207926g	4.6	2.1	1.4	71.1	1	0	2	2	2			2	0	0	0	0	0	3	1	4
117	226317g	5.4	5.1	3.1	3.7	0	0	1	4	4			2	2	1	1	0	0	3	3	5
118	499972f	4.6	4.5	3.5	3.9	0	0	1	3	3	2	2	2	2	0	0	0	0	3	3	4
119	496467f	11	11	0	0	0	0	1	3	4	3		2	2	0	0	0	1	3	4	5
120	601090f	6.6	3.8	2.2	1.1	0	0	2	3	3	4	3	1	0	0	0	0	0	3	2	2
121	042071g	6.3	5.4	0	0	0	0	2	3	3	3	1	2	1	1	0	0	0	3	3	4
122	335922f	1.5	1.2	0	0	1	1	1	2	2			2	2	0	0	0	0	3	3	1

123	357562 f	10	11	0	0	0	0	1	4	4			2	2	1	1	1	1	4	4	5
124	142308 f	3.3	3.1	5.8	6.2	0	1	2	3	2	2		2	1	1	0	0	0	3	3	4
125	380665 f	5.7	5.2	0	0	0	0	2	4	4			2	2	1	1	0	0	3	3	4
126	140644 g	4.8	4.5	4	4.4	0	0	2	3	3	3	3	2	0	1	1	0	0	3	2	2
127	774839 f	5.5	5.2	0.9	1.2	0	0	2	3	3	4	3	2	2	1	0	0	0	3	3	4
128	780237 f	7.5	5.4	0	0	0	0	2	4	4			2	0	1	1	0	0	3	2	3
129	806825 f	5.4	5.4	0	0	0	0	1	4	4			2	2	1	1	0	0	3	3	5
130	833441 f	7.5	7.5	0	0	0	0	1	3	3	4	4	2	2	1	1	0	0	3	3	5
131	189560 g	4.6	4	0	0	0	0	1	3	3	3	3	2	2	1	1	0	0	3	3	4
132	163445 g	3.2	2.3	0	0	0	0	2	3	3	3	2	1	0	0	0	0	1	3	4	3
133	140374 g	6.2	4.1	0	0	0	0	2	4	3		3	2	1	1	1	0	0	3	3	3
134	779234 f	4.1	3.9	0	0	0	0	1	4	3		2	2	1	1	1	0	0	3	3	4
135	887876 f	3.9	3.7	0	0	0	0	1	3	3	3	2	2	0	0	0	0	0	3	2	4
136	888452 f	6.2	5.9	4.4	4.8	0	0	3	4	4			2	1	0	0	0	0	3	3	4
137	287766 f	4.6	3.9	2.6	3.4	0	1	2	3	3	3	1	0	0	0	0	0	0	2	2	2
138	300302 f	4.8	2.5	0	0	0	0	2	3	2	1		1	1	0	0	0	0	3	3	3

139	067487 f	6.2	6	7	7.2	0	0	1	3	4	3		1	0	1	1	0	0	3	2	5
140	845860 d	8	5	1.9	2.1	0	0	1	4	4			1	0	1	1	0	0	3	2	4
141	037234 f	6.7	6.5	2.2	2.3	0	0	1	3	3	3	3	1	0	1	1	0	0	3	2	4
142	387301 f	9.6	7.6	4.5	5.5	0	0	2	4	3		4	2	1	1	1	0	0	3	3	4

KEY:

ID- Serial number ; HOSPI – Hospital number ; SEX: 0=female; 1=male
HISTO (Histology): 1=addenocarcinoma;2=mucinous adenicarcinoma;3=signet ring cell cancer
GRADE (Histological grade of tumor):1=1=well differentiated; 2= moderately differentiated; 3= poorly differentiated
NEORX (Type of neoadjuvant therapy):1=shot course therapy; 2=long course chemoradiation;3=radical chemoradiation;4=chemotherapy alone
CHEMO (Whether concurrent chemotherapy is administered):0=no;1=yes ; RTDOSE = Total dose of RT received expressed in Gy
TIME (Time interval between last day of neoadjuvant therapy and imaging):1=< 6 weeks; 2=6-8weeks; 3=8-10 weeks
TYPE (Type of tumor):1=circumferential;2=hemicircumferential;3=polypoidal ; LOCN(Tumor location):1=upper rectum;2=mid rectum;3=low rectum)
HI (Involvement of upper rectum by tumor):0=no;1=yes ; MID(Involvement of mid rectum by tumor):0=no;1=yes)
LOW (Involvement of low rectum by tumor):0=no;1=yes) ; PBREC(Involvement of levator ani in low rectal tumor):0=no;1=yes
IAS(Involvement of internal anal sphincter in low rectal tumor):0=no;1=yes ; EAS(Involvement of external anal sphincter in low rectal tumor):0=no;1=yes
IRF (Involvement of ischiorectal fossa in low rectal tumor):0=no;1=yes ; ADJ(Involvement of adjacent structures in low rectal tumor):0=no;1=yes
LEN1 (Tumor length in pre-treatment MRI):expressed in cm ; LEN2(Tumor length in post-treatment MRI):expressed in cm
DIST1(Distance of lower edge of tumor from anorectal junction in cm; DIST2(Distance of lower edge of tumor from anorectal junction in cm)
CRM1 (CRM in pre-treatment MRI):0=positive;1=negative ; CRM2(CRM in post-treatment MRI):0=positive;1=negative
T2SIG (T2 signal intensity of tumor):1=high;2=intermediate;3=low
TS1(T stage of tumor in pre-treatment MRI):1=T1,2=T2,3=T3;4=T4 ; TS2(T stage of tumor in post-treatment MRI):1=T1,2=T2,3=T3;4=T4
T3S1 (T3 stage of tumor in pre-treatment MRI):1=T3a,2=T3b,3=T3c,4=T3d ; T3S2(T3 stage of tumor in post-treatment MRI):1=T3a,2=T3b,3=T3c,4=T3d
NPRE(N stage in pre-treatment MRI):1=N1,2=N2 ; NOST(N stage in post-treatment MRI):1=N1,2=N2
EM1 (EMVI in pre-treatment MRI):0=negative,1=positive ; EM1(EMVI in post-treatment MRI):0=negative,1=positive
MPRE (M stage in pre-treatment MRI):0=M0,1=M1 ; MPOST (M stage in post-treatment MRI):0=M0,1=M1
STG1 (TNM stage in pre-treatment MRI)1=Stage1,2=stage2,3=stage3,4=stage 4
STG2 (TNM stage in post-treatment MRI)1=Stage1,2=stage2,3=stage3,4=stage 4
TRG (MRI Tumor Regression Grade in post-treatment MRI):1=TRG1, 2=TRG2, 3=TRG3, 4=TRG4,5= TRG5

ABBREVIATIONS:

ADC: Apparent Diffusion Coefficient

CT: Computed Tomography

CRM: Circumferential Resection Margin

DWI: Diffusion Weighted Imaging

EMVI: Extramural Vascular Invasion

HR: High Resolution

IRB: Institutional Review Board

MERCURY: Magnetic Resonance Imaging and Rectal Cancer European Equivalence

MRI: Magnetic Resonance Imaging

SPAIR: Spectral Attenuated Inversion Recovery

TE: Echo Time

TR: Repetition Time

TME: Total Mesorectal Excision

TRG: Tumor Regression Grade